

ABSTRACTS

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IN VIVO VASCULAR HYPOREACTIVITY IN THE MESENTERIC ARTERY OF RATS WITH CIRRHOSIS : REVERSED BY OCTREOTIDE. I. Colle (1), A. Geerts (1), A. De Vriese (3), H. Van Vlierberghe (1), N. Lameire (23), M. De Vos (1). (1) Dept of Hepato-Gastroenterology ; (2) Dept of Nephrology, Ghent University Hospital.

Background : Cirrhosis is complicated by a splanchnic vasodilation and hyporeactivity towards vasodilators and vasoconstrictors. Octreotide may influence these haemodynamic disturbances.

Aim : The *in vivo* response of mesenteric arteries to different vasoactive agents was studied in experimental animals with cirrhosis, treated with octreotide long acting release (LAR) or with placebo.

Methods : One week after a single dose of octreotide LAR (10mg/kg) or placebo given SC, 2 groups of animals were sham-operated (sham_{octreo}, n=8 ; CBDL_{plac}, n=7), and secondary biliary cirrhosis was induced by common bile duct ligation in a third and fourth group (CBDL_{octreo}, n=9 ; CBDL_{plac}, n=8). Four weeks after surgery, haemodynamics and mesenteric blood flow (MBF) were measured during infusion of the endothelium-dependent vasodilator acetylcholine (ACh), the NO donor deta-NONOate and the potassium channel opener pinacidil directly in the mesenteric artery.

Results : Baseline mean arterial pressure (MAP) was significantly higher in both sham rats compared to the CBDL_{plac}. The administration of octreotide resulted in a significant increase in MAP : the CBDL_{octreo} group (109±13 mmHg) had a significantly higher MAP than CBDL_{plac} (93±8 mmHg) and reached the same values as the CBDL_{plac} group (109±16 mmHg). Baseline MBF was significantly higher in CBDL_{plac} than in both sham groups. The MBF response to ACh, detaNONOate and pinacidil was significantly lower in CBDL_{plac} than in both sham groups, while the CBDL_{octreo} group had a normal MBF response, which was not different from both sham groups.

Conclusion : This *in vivo* study demonstrates an impaired response to endothelium-dependent and endothelium-independent vasodilators in the mesenteric artery of experimental animals with cirrhosis. This hyporeactivity is prevented and/or restored by the early administration of octreotide LAR. This suggests an abnormality in the vascular smooth muscle cells of the mesenteric artery, which can be influenced by octreotide. Administration of octreotide was able to normalise arterial blood pressure and tended to decrease MBF in cirrhotic rats. Further study to explore the possible beneficial effect of long acting octreotide on splanchnic and systemic haemodynamics should be performed.

LEUKOCYTE RECRUITMENT IS IMPAIRED IN THE PERITONEAL MICROCIRCULATION OF RATS WITH PORTAL HYPERTENSION AND CIRRHOSIS. A. Geerts (1), I. Colle (1), A. De Vriese (2), S. Mortier (2), H. Van Vlierberghe (1), N. Lameire (2), M. De Vos (1). (1) University Hospital Ghent, Dpt of Hepatogastroenterology ; (2) University Hospital Ghent, Dpt of Nephrology.

Background : Patients with liver cirrhosis and portal hypertension (PHT) are predisposed to develop spontaneous bacterial peritonitis. The recruitment of a circulating leukocyte in response to an infectious stimulus is mediated by adhesive interactions between the leukocyte and the venular endothelium. Leukocyte rolling is followed by firm adhesion and extravasation.

Aim : The aim of the study is the *in vivo* evaluation of leukocyte behavior in the peritoneal microcirculation after LPS exposure in rats with portal hypertension and cirrhosis.

Methods : The microcirculation of the rat visceral peritoneum was visualized by intravital microscopy in control (n=8), Sham (n=8), partial portal vein ligated (PPVL) (n=8) and common bile duct ligated rats (CBDL) (n=8). The peritoneum was superfused with a buffer solution (EBSS). The number of rolling, adhering and extravasated leukocytes was counted at different time intervals after exposure to 1 µg/ml LPS dissolved in the superfusion fluid.

Results : Baseline leukocyte rolling, adhesion and extravasation was not significantly different between the control, Sham, PPVL and CBDL rats. In control and Sham rats, infusion of LPS 1µg/ml resulted in a significantly increase in the number of rolling, adhering, and extravasated leukocytes (P<0.005). There was no difference between control and Sham rats. In PPVL rats, there was a minor increase in the leukocyte rolling over time and also the number of adhering and extravasated leukocytes increased modestly. Also in CBDL rats, the number of rolling, adhering and extravasated leukocytes increased modestly. PPVL and CBDL rats showed a significantly impairment in leukocyte rolling (P<0.001 at t=120min), adhesion (P<0.001 at t=120min) and extravasation (P<0.001 at t=120min) compared with control and Sham rats.

Conclusion : In this animal model of cirrhosis and PHT, there is an impairment of leukocyte response to an endotoxin. PHT alone, without liver insufficiency, is able to induce these changes. Alterations in leukocyte recruitment in PPVL and CBDL rats may explain the increased susceptibility to infections, especially spontaneous bacterial peritonitis.

INTESTINAL BACTERIA AS A KEY FACTOR FOR ALCOHOLIC LIVER DISEASE IN MICE. T. Gustot (1), A. Lemmers (1), E. Quertinmont (2), H. Louis (1), O. Le Moine (1), J. Devière (1). (1) Dept Gastroenterology, Erasme Hospital, Brussels ; (2) Laboratory of Experimental Gastroenterology.

Introduction : Gut microflora is important in the pathogenesis of alcoholic liver diseases (ALD). Alcohol consumption induces an increase of intestinal permeability to bacterial compounds (*LPS*). These molecules activate Kupffer cells via *Toll-like receptor 4* (TLR4) associated with CD-14 and induce inflammation in the liver.

Aims : To study the effect of EtOH, EtOH plus gut decontamination on intestinal bacteria, severity of liver damages and TLR expression in the liver.

Methods : C57B16 mice were fed by a modified Lieber-De Carli liquid EtOH or control diet for 10 days. Plasma alanine aminotransferase (ALT), histology and RT-PCR of TNF α , TLR1 to 9 gene expression were determined from liver samples. The evaluation of bacterial overgrowth were assessed by 48h quantitative anaerobic culture. The gut decontamination were performed by addition of neomycine (350mg/l) and metronidazole (600mg/l) to the liquid diet. The total intestinal transit time was assessed by gavage of red carmine-methylcellulose and appearance of red in the saddle.

Results : EtOH exposure induced an increase of liver weight, ALT, a macrovacuolar steatosis, an up-expression of mRNA TNF α , TLR1, TLR2, TLR4, TLR5 and TLR6 in the liver. EtOH induced a bacterial overgrowth in the jejunum and the colon. The EtOH increased clearly the total intestinal transit time. The addition of antibiotics to EtOH liquid diet reduces the liver weight, ALT, the steatosis score, the hepatic mRNA of TNF α , TLR4, TLR5 and TLR6.

Conclusions : The EtOH liquid diet induces an intestinal bacterial overgrowth, which could be explained by a slowing of intestinal transit time, and an up-regulation of some bacterial pattern-recognition receptors in the liver. The gut decontamination clearly reduces the severity of the disease.

CURCUMIN INHIBITS EARLY NF-KB ACTIVATION AND IMPROVES EXPERIMENTAL STEATO-HEPATITIS IN MICE. I. Leclercq, Ch. Sempoux, V. Lebrun, G. Farrell, Y. Horsmans. Gastroenterology Unit, Cliniques Universitaires UCL-St-Luc, Brussels.

Clinical and experimental research suggests the involvement of oxidative stress in the pathogenesis of non-alcoholic steatohepatitis (NASH). The goal of this study was to determine the role of NF- κ B redox-sensitive signalling pathways in recruitment of inflammation in fatty liver disease.

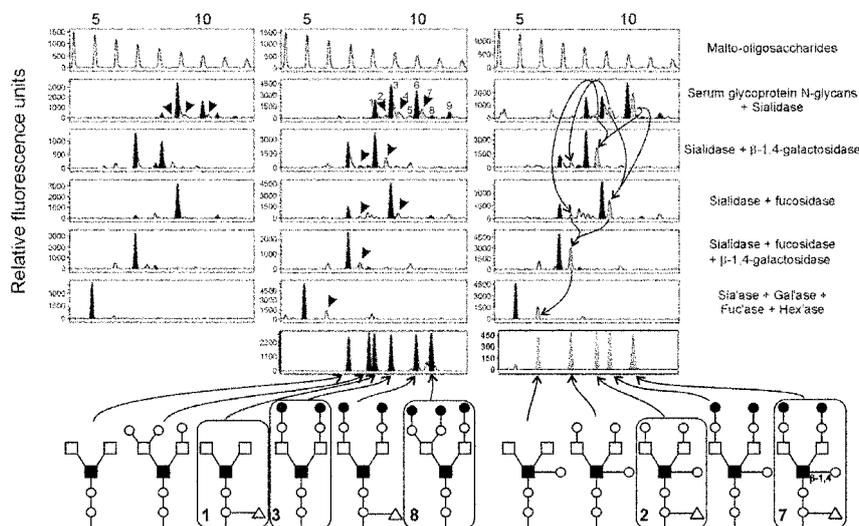
Methods : C57B16/J mice were fed the methionine and choline deficient (MCD) or the control diet, supplemented or not with the NF- κ B inhibitor Curcumin (1% w/w) for 4 weeks.

Results : MCD diet induced hepatic macrovesicular steatosis, intralobular inflammation and stimulation of fibrogenesis as shown by a 4-fold increased of type I collagen mRNA, together with a 10-fold rise in serum ALT and severe intrahepatic oxidative stress (50-fold increased in hepatic lipid peroxides). EMSA demonstrated sustained activation of NF- κ B (6.1 \pm 1.4 OD vs 0.2 \pm 0.4 in controls), associated to a 2 to 3-fold increased in ICAM-1, COX-2, and MCP-1 mRNA, all NF- κ B-responsive genes with pro-inflammatory properties. To test whether inflammatory reaction in fatty liver disease is mediated by NF- κ B, the NF- κ B inhibitor curcumin was administered together with the MCD diet. Curcumin significantly reduced hepatic inflammation, serum ALT (by 40%) and collagen mRNA expression (by 50%) but had no effect on steatosis or on the level of hepatic lipid peroxides (1710 \pm 750 vs 2250 \pm 560 nmol/g liver in MCD/Curcumin vs MCD). Importantly, curcumin prevented the activation of NF- κ B induced by the MCD diet (0.7 \pm 1 vs 6.1 \pm 1.4 OD in MCD/Curcumin vs MCD ; p<0.001), as well as the down stream activation of ICAM-1, COX-2 and MCP-1. Consistent with the operation of oxidative stress, MCD-diet increased stress-reactive AP-1 binding activity and dependent heme-oxygenase-1 protein expression. This was not altered by dietary curcumin.

Conclusion : experimental steatohepatitis is associated with marked oxidative stress, activation of stress-responsive transcription factors and down stream activation of pro-inflammatory mediators. Blockade of NF- κ B activation and dependent pro-inflammatory genes reduced the severity hepatic inflammation. Thus, NF- κ B pathway appears as one, but not the unique, pathway by which oxidative stress mediated recruitment of inflammation in fatty liver disease.

NONINVASIVE DIAGNOSIS OF LIVER CIRRHOSIS USING DNA-SEQUENCER-BASED TOTAL SERUM PROTEIN GLYCOMICS. N. Callewaert (1), H. Van Vlierberghe (2), A. Van Hecke (1), W. Laroy (1), J. Delanghe (3), R. Contreras (1). (1) Dpt of Molecular Biomedical Research, Ghent University and Flanders Interuniversity Institute for Biotechnology ; (2) Dpt of Gastroenterology, Ghent University Hospital ; (3) Dpt of Clinical Chemistry, Microbiology and Immunology.

We developed a 'clinical glycomics' method that uses a PCR thermocycler and a DNA sequencer/fragment analyser to rapidly generate high-resolution profiles of the N-glycan post-translational modifications present on the proteins in patient's serum (see the Figure of this abstract). We have found that the serum N-glycome yields a biomarker that diagnoses mild liver cirrhosis with 90% efficiency (and advanced liver cirrhosis with 100% efficiency). Highly specific serum biomarkers such as the one described here are very valuable, as they can help to obviate the biopsy need in a lot of cirrhosis patients. Moreover, this biomarker could eventually be used in routine follow-up of chronic liver disease patients, to yield an early warning signal that cirrhosis has developed and that complications (amongst others : hepatocellular carcinoma) might arise. Our biomarker can easily be implemented in the majority of the existing molecular diagnostics laboratories at low cost.



SUPPRESSION OF DNA-REPAIR BY HEPATITIS C VIRUS CORE PROTEIN AFTER TRANSFECTION INTO HUMAN LIVER CELLS : POSSIBLE ROLE IN THE DEVELOPMENT OF HCC. T. Severi (1), T. Crabbé (2), A. Van Eetveldt (1), C. Verslype (1), T. Roskams (2), J. Fevery (1), J.F van Pelt (1). (1) Department of Liver and Pancreatic Diseases, University Hospital Gasthuisberg, Leuven, Belgium ; (2) Department of Morphology and Molecular Pathology, University Hospital Gasthuisberg, Leuven, Belgium.

Introduction : Several studies have documented the important association between HCV infection and hepatocellular carcinoma. The mechanisms involved are still unknown and could involve viral proteins. We studied the influence of HCV-core on DNA-repair after UV-induced DNA damage, cell proliferation and telomerase activity.

Methods : We have developed stably transfected HepG2 cell lines that express HCV core protein (genotype 1b) and a HCV core variant with truncation of the two C-terminal hydrophobic domains. Cell lines were characterized for gene expression by RT-PCR and protein localization by immunohistochemistry. To study the DNA repair, cells were seeded at 5,000 cells/well in 96-well culture plates. The next day, the cells were UV radiated (14 J/cm²) and cultured for 3 additional days after which time an XTT-assay was performed. We calculated the reduction in cell number per well with or without UV-exposure for the different cell lines (HCV core and control lines : HBsAg-, HBx- or mock-transfected).

Results : HCV core-transfected cells were significantly less capable to repair the DNA damage than control cells or cells expressing truncated core. Interestingly, expression of the full length HCV core did increase the cell doubling time in one of the cell lines. Therefore we investigated apoptosis and telomerase activity in these cells.

Conclusion : The suppression of DNA repair by HCV core protein renders the cells more sensitive to acquire mutations that in combination with enhanced in vivo cell turnover in the infected liver might increase the likelihood of malignant transformation of HCV-infected cells by other viral factors or upon exposure to environmental factors (food, drugs, smoking, alcohol etc). This could be one of the early steps contributing to the development of HCV-related HCC. Further studies are required to determine for which phase of the developmental process of HCV-induced HCC our cells can be used as model.

INCREASED ANGIOGENESIS AND PERMEABILITY IN THE PERITONEAL MICROCIRCULATION OF RATS WITH CIRRHOSIS AND PORTAL HYPERTENSION. A. Geerts (1), I. Colle (1), A. De Vriese (2), S. Mortier (2), H. Van Vlierberghe (1), N. Lameire (2), M. De Vos (1). (1) Dpt of Hepatogastroenterology ; (2) Dpt of Nephrology, University Hospital Ghent, Belgium.

Background : Portal hypertension (PHT) is characterized by splanchnic arterial vasodilation. Several functional alterations causing this vasodilation have been proposed. Little is known about the role of structural vascular changes in this vasodilatory state. Cirrhosis with PHT is also associated with the formation of collaterals and ascites. Alterations in the peritoneal microcirculation may be implicated in the formation of ascites.

Aim : The aim is to evaluate the in vivo microvascular density and permeability in the peritoneal microcirculation of rats with cirrhosis and PHT.

Methods : The microvascular density and permeability was visualized by intravital microscopy in control rats (n=6), partial portal vein ligated rats (PPVL) (n=6) and common bile duct ligated rats (CBDL) (n=6). To evaluate peritoneal microvascular density, a segment of the distal ileum proximal to the caecum was recorded at random. The total vessel length (cm/cm^2) was determined. The microvascular permeability was studied in a peritoneal venule using fluorescein isothiocyanate albumin (FITC-albumin, 50mg/kg). Leakage of FITC-albumin was defined by the change of the ratio between the grey scale within the vessel and the grey scale value in the interstitium.

Results : Microvascular density is increased in PPVL ($408 \pm 109 \text{ cm}/\text{cm}^2$) and CBDL rats ($1027 \pm 243 \text{ cm}/\text{cm}^2$) compared with control rats ($122 \pm 44 \text{ cm}/\text{cm}^2$) ($P=0.03$; $P=0.004$, respectively). CBDL rats had also significantly higher microvascular density than PPVL rats ($P=0.04$). The hyperpermeability for albumin increased over time in CBDL rats (1.4 ± 0.03 at $t=0\text{min}$ vs 1.1 ± 0.02 at $t=60\text{min}$) (p ($P=0.001$; $P=0.05$, respectively).

Conclusion : Microvascular density was significantly increased in PPVL and CBDL rats, implicating an increased effective vascular surface area. This splanchnic angiogenesis may partly contribute to the splanchnic vasodilation in portal hypertension and cirrhosis. In addition, macromolecular leakage was significantly higher in CBDL rats than in control and PPVL rats. This hyperpermeability to macromolecules in cirrhotic rats, which is not present in PPVL rats, may be one of the reasons why ascites develops in cirrhotics and not in a pure portal hypertension model as in humans, despite an increased angiogenesis in both models.

SYMPATHETIC NERVOUS SYSTEM INHIBITION IN ACUTE AND CHRONIC CCL4 INTOXICATION, RESULTS IN INHIBITION OF HEPATIC STELLATE CELLS/MYOFIBROBLASTS AND STIMULATION OF HEPATIC PROGENITOR CELLS. N. Sinelli (1), D. Cassiman (1), L. Dubuisson (2), G. De Hertogh (1), J. Fevery (1), J. Rosenbaum (2), T. Roskams (1). (1) University of Leuven-Belgium ; (2) Groupe de Recherches pour l'Etude du Foie, Université V. Segalen Bordeaux2, Bordeaux, France.

Both progenitor cells and hepatic stellate cells express of neural / neuroendocrine features. Aim : to investigate whether these cell types are under the control of the nervous system. We recently showed that, prazosin (alpha-1-adrenergic inhibitor) treatment in acute galactosamine intoxicated rats resulted in progenitor cell (PC) stimulation, while the number of hepatic stellate cells/myofibroblasts (HSC/MF) decreased (Hepatology, 2003, 38, 783A). In the present study, we investigated the effect of toxic sympathectomy by 6- hydroxydopamine (OHDA) and of alpha1-adrenergic receptor antagonist (prazosin) after 96h (n=12), 2 weeks (n=12) and 6 weeks CCl4-intoxication in the rat. We performed immunohistochemistry using antibodies for HSC/MF markers desmin and GFAP and for PC marker OV-6. The number of HSC/MF and PC was counted in five randomly selected microscopic fields (magnification 400x) in each animal. Sympathetic nervous system inhibition (with 6-OHDA, as well as prazosin) after CCl4 intoxication in the rat resulted in a significantly lower number of GFAP-reactive HSC/MF at all time points (Mann-Whitney test $p < 0.05$). The number of desmin-reactive HSC/MF was not significantly different at 96 h while it was significantly lower at 2 weeks and 6 weeks ($p < 0.05$). The number of PC was significantly higher at all time points. Sympathetic nervous system inhibition in acute as well as chronic (with advanced fibrosis) CCL4 intoxication results in a significant lower number of HSC/MF and a higher number of PC. This opens interesting therapeutical perspectives for as well acute as chronic liver diseases, using Prazosin, which is a well tolerated drug.

SOMATOSTATIN REDUCES MIGRATION OF HUMAN HEPATOMA CELLS AND HEPATIC STELLATE CELLS VIA SOMATOSTATIN RECEPTOR SUBTYPE 1. H. Reynaert (1), K. Rombouts (2), A. Vandermonde (2), D. Urbain (1), U. Kumar (3), M. Pinzani (4), P. Bioulac-Sage (5), J. Rosenbaum (6), A. Geerts (2). (1) Division of Gastroenterology-Hepatology, University Hospital, Free University of Brussels (VUB); (2) Laboratory for Molecular Liver Cell Biology, Free University of Brussels (VUB); (3) Department of Medicine, Royal Victoria Hospital, McGill University, Montreal, Canada; (4) Dipartimento di Medicina Interna, Università degli Studi di Firenze, Firenze, Italy; (5) Pathology Department, University Hospital, Bordeaux, France; (6) Groupe de Recherche pour l'Etude du Foie, INSERM E0362 and IFR 66, Université Victor Segalen, Bordeaux 2, France.

Background and aims : In a previous study, we described the expression of somatostatin receptor (SSTR) subtypes in human cirrhosis and HCC : both hepatocytes and hepatic stellate cells (HSCs) expressed SSTRs. The aim of the present study was to examine the *in vitro* effect of selective SSTR subtype agonists on proliferation, apoptosis and migration of hepatoma cell lines (HepG2, HuH7) and human HSCs.

Methods : The effect of specific SSTR subtype agonists L-797,591, L-779,976, L-796,778, L-803,087 and L-817,818 (agonists of SSTR subtypes 1- 5, respectively) on proliferation and apoptosis of HepG2, HuH7 and HSCs was assessed by BrdU and by TUNEL method, respectively. The influence of SSTR agonists on migration of tumor cells and HSCs was investigated using Boyden migration chambers.

Results : None of the 5 somatostatin agonists reduced proliferation or induced apoptosis of hepatoma cells or HSCs. However, as compared to untreated control cells, L-797,591, a specific SSTR1 agonist, reduced migration of HepG2, HuH7 and HSCs significantly to 88% +/- 7% (P<0.05), 83% +/- 11% (P<0.05) and 67% +/- 13% (P< 0.01), respectively.

Conclusions : Although cirrhotic liver and HCC express SSTRs, specific somatostatin agonists had no significant effects on proliferation and apoptosis. However, somatostatin may decrease invasiveness of HCC by reducing migration of hepatoma cells and/or HSCs via stimulation of SSTR subtype 1. Our findings may explain some of the negative results of recent clinical trials evaluating somatostatin analogues for the palliative treatment of HCC. Before starting new clinical trials with somatostatin analogues, these findings should be taken into account. *Acknowledgement* : Merck Research Laboratories, Rahway, NJ, USA for providing SSTR agonists.

AUTOIMMUNE HEPATITIS IN THE ELDERLY, COMPARISON WITH A YOUNGER POPULATION. C. Verslype, C. George, W. Van Steenberghe, F. Nevens, P. Yap, J. Fevery. Hepatology, KU Leuven/UZ Gasthuisberg, Leuven.

Out of a series of 112 patients with AIH, 28 were ≥ 65 years at the time of diagnosis. They are compared with the younger age group. In general, the incidence of AIH was nearly similar at all age decades studied (10-15 females, 5 males per decade) and there were only mild differences between the 2 groups : Gender M :F 1 :3 (≥ 65) vs 1 : 2 (<65 yr). The presenting symptoms in those ≥ 65 yr were incidental finding in 9 % (vs 20 %), fatigue in 23 % (vs 30 %), jaundice 40 % (vs 48%), jaundice + complications 18 % (vs 5%), ascites 9 % (vs 4 %). ANA $\geq 1/80$ was pos in 87 % (vs 86 %), SMA $>1/40$ pos in 64% (vs 81 %) aLKM always neg (vs 3 %). Histological assessment showed acute necrotising hepatitis (collapse) in 27 % (vs 16 %), subacute, severe interphase hepatitis in 18 % (vs 25%), chronic hepatitis with plasmolympocytic infiltrate in 22 % (vs 32 %), cirrhosis in 23 % (vs 27 %) and biopsy refused in 11 %. Importantly the elderly patients responded very well to lower doses of methylprednisolone (6-8 mg)+ azathioprine (1 mg/kg) obviating side effects seen with the higher dosages such as infectious complications leading e.g. to sepsis and death in some patients. In conclusion, AIH is also frequent in the elderly population and presents with quite similar symptoms and signs. Acute necrotising hepatitis with complicated jaundice seems somewhat more common. The steroid therapy should be kept at a low dose.

THE MOLECULAR ADSORBENT RECYCLING SYSTEM (MARS) IMPROVES HEMODYNAMIC DISTURBANCES IN PATIENTS WITH PORTAL HYPERTENSION AND ACUTE-ON-CHRONIC ALCOHOLIC LIVER FAILURE : RESULTS OF A RANDOMIZED CONTROLLED STUDY. W. Laleman(1), F. Nevens (1), A. Wilmer (2), P. Evenepoel (3), Z. Zaman (4), M. Zeegers (1), I. Vander Elst (1), C. Verslype (1), J. van Pelt (1), J. Fevery (1). (1) Hepatology, KU Leuven/UZ Gasthuisberg, Leuven ; (2) Medical Intensive Care Unit, KU Leuven/UZ Gasthuisberg, Leuven ; (3) Nephrology, KU Leuven/UZ Gasthuisberg, Leuven ; (4) Laboratory Medicine, KU Leuven/UZ Gasthuisberg, Leuven.

Background : Circulatory dysfunction in cirrhosis is presumed to originate in excessive endogenous vasoactive substances. We aimed at clarifying the effect and mechanism of MARS on systemic hemodynamics in patients with AoCLF. **Methods** : 12 patients (mean HVPG 19 ± 1 , MELD 23 ± 2) were randomised to standard medical therapy (SMT) (n=6), or MARS with SMT (n=6) over a 3 to 5 day study period with a further 7 day follow-up. 2 patients in the SMT group did not reach the end-point and were excluded. Besides hemodynamic monitoring before and after sessions, plasma and dialysate levels (out of MARS circuit) of vasoactive hormones were measured.

Results : MARS treatment resulted in improved hemodynamics (mean % change MAP $+16.5 \pm 6.7\%$ vs $-12.4 \pm 5.8\%$ after SMT, $P=0.05$; SVRI $+14.3 \pm 5.8\%$ vs $-7.3 \pm 2.9\%$ after SMT, $P=20.1 \pm 19.9\%$ after SMT, $P=4.6 \pm 19.7\%$, P Positive correlations were found after MARS between change in SVRI and respectively the dialysate concentration of nitrate/nitrite and serum renin levels ($p=0.048$ and 0.004).

Conclusion : Treatment with MARS improves systemic hemodynamics by a decrease in endogenous vasoactive substances, in accordance with the current hypothesis of the pathogenesis of portal hypertension.

BELGIAN MULTICENTER RANDOMISED STUDY : INTERIM ANALYSIS OF COMPARISON OF ONE YEAR PEGINTERFERON ALFA-2B (PEGINTRON) PLUS RIBAVIRINE (REBETOL) VERSUS NO TREATMENT IN PATIENTS WITH CHRONIC HEPATITIS C AND PERSISTENTLY NORMAL ALT LEVELS. L. Lasser (1), P. Langlet (2), J. Mulkay (3), M. Adler (4), I. Colle (5), H. Van Vlierberghe (5), N. Boon (4), H. Louis (4), EM. Talib (1), C. De Galocsy(6), A. Reeckmans(7). (1)CHU Brugmann Brussels ; (2) CHU Brugmann/CHIREC Brussels ; (3) CHU St Pierre Brussels ; (4) ULB Erasme Brussels ; (5) UZ Gent ; (6) St. Anne-St. Rémi Brussels ; (7) ASZ Aalst.

Background/Aims : About 25 to 30 percent of patients with chronic hepatitis C have persistently normal ALT levels. Until now consensus is not to treat those patients outside of study protocols. However, several studies showed that 20 to 25 percent of patients with normal transaminases have significant fibrosis.. Recently a large multicentric study was presented at the 2003 AASLD meeting showing that response rates with pegylated IFN alfa-2a and ribavirine combination therapy in patients with normal transaminases are comparable to patients with elevated transaminases.

Methods :A prospective Belgian multicenter randomised open trial was designed and is still ongoing. Naïve chronic HCV patients with persistently normal ALT levels (defined as at least three assays within normal range over a minimum of 6 months) are randomised between treatment arm (pegintron $1.5 \mu\text{g}/\text{kg}/\text{week}$ plus ribavirine 800, 1000 or 1200 mg/day) and control arm (no treatment). Proportion of end of treatment and sustained virological response rates are determined. Histological evolution will be assessed by a liver biopsy at screening and 2 and 5 years after randomisation.

Results : Currently, 27 patients have been included and 12 patients were randomised in the treatment arm. After 6 months of treatment 6 of 10 patients had negative PCR. Until now 7 patients completed 48 weeks of treatment. One patient stopped treatment because of adverse events (8,33%). Three patients (43 %) presented a virological end of treatment response. Concerning transaminase levels no significant differences were found between both groups during the 48 weeks of treatment. Only one patient in the treatment group presented a very moderate flare up with ALT levels staying below two times upper limit of normal. At baseline moderate fibrosis F2 (Metavir score) was found in 9 patients (36%). No results on histological evolution are available at this moment.

Conclusion : In patients with chronic HCV and persistently normal transaminases combination therapy with peginterferon alfa-2b plus ribavirin seems to be safe and beneficial regarding end of treatment virological response. Final results have to be evaluated in a larger sample of patients to confirm that in HCV+ patients with persistently normal ALT levels antiviral IFN therapy might be indicated according to the results of genotype and stage of fibrosis.

THE VALUE OF NON-INVASIVE TOOLS TO DIAGNOSE HCC OR PRE-MALIGNANT DYSPLASTIC NODULES IN PATIENTS WITH ADVANCED CIRRHOSIS AND A HEPATIC MASS. F. Nevens(1), M. Sorour (1), C. Verslype (1), L. Libbrecht (2), D. Vanbeckevoort (3), D. Billen (3), R. Aerts (4), J. Fevery (1), T. Roskams (2), J. Pirenne (4). (1) Hepatology, KU Leuven/UZ Gasthuisberg, Leuven ; (2) Histopathology, KU Leuven/UZ Gasthuisberg, Leuven ; (3) Radiology, KU Leuven/UZ Gasthuisberg, Leuven ; (4) Abdominal Transplantation Surgery, KU Leuven/UZ Gasthuisberg, Leuven.

Background : Current imaging techniques often detect lesions. Organ share organisation offers pts with suspicion of HCC without biopsy proof priority. Dysplastic nodules (Dyspl) are considered as premalignant.

Methods : In a prospective cohort study the value of NMR and \pm fetoprotein AFP to detect HCC and/or Dyspl was explored in pts waiting for LT (n=200) of which 51 had HCC and 23 isolated Dyspl on histology.

Results : HCC was suspected on NMR in 59 pts, this was confirmed in 45 pts, 4 pts had only Dyspl (+ predictive factor (PPF) for HCC or Dyspl 76%). Elevated AFP (> 20 μ g/ml) was found in 37 pts : 24 had HCC, 7 Dyspl PPF (84%) ; In postalcoholic/cryptogenic cirrhosis (n=85) with elevated AFP (n=9), 8 had HCC and 1 Dyspl ; in viral cirrhosis (n=77). 12 had isolated dysplasia : 6 had AFP. Cirrhotics with suspicion on NMR of HCC and elevated AFP (n=25) : 23 had HCC and 1 Dyspl (PPF for HCC or Dyspl : 92%).

Conclusion : 50% of the Dyspl in viral cirrhosis secrete AFP vs none in alcohol/cryptogenic cirrhosis. Elevated AFP is highly predictive for HCC in case of postalcoholic/cryptogenic cirrhosis. The PPF of NMR and elevated AFP for the presence of HCC and Dyspl is extremely high.

PRETRANSPLANT MELD SCORE COMPARED TO CHILD-PUGH SCORE AS PREDICTOR OF OUTCOME ON THE LIVER WAITING LIST BUT NOT AFTER LIVER TRANSPLANTATION. M. Adler (1), P. Vereerstraeten (2), N. Bourgeois (1), N. Boon (1), H. Louis (1), M. Gelin (1), B. Ickx (3), V. Donckier (1). (1) Medico-Surgical Department of Hepato-Gastroenterology ; (2) Department of Nephrology ; (3) Department of Anesthesiology, Hopital Erasme, ULB, Brussels.

MELD score is now implemented in the US for liver allocation but it has not been validated in Europe and its association with post-transplant (PTX) outcome is unclear. Optimal cut-off values of MELD and C-Pugh scores predicting death on the liver waiting list were defined in a series of 124 cirrhotic patients listed for liver transplantation. Six month actuarial survival while on the waiting list is 90% with a C-Pugh < 11 and MELD < 17 whereas it decreased progressively down to 40%, 6 months after listing for those having a C-Pugh and MELD score > 10 and > 16. Analysis of a series of 112 patients (85 chronic liver disease and 27 hepatocellular carcinoma) reveal no change of MELD value at time of transplantation compared to the score at time of listing (mean \pm SD : 15.5 \pm 7.7 vs. 15 \pm 5.8) with a mean waiting time of 118 days. Using either the optimal cut-off for MELD score (< 17 or > 16) or 7 different strata (3 to 7, 8 to 10, 11 to 13, 14 to 16, 17 to 19, 20 to 22, 23 to 39), whether measured at listing or just before liver transplantation, there was no significant difference (χ^2 4.97, p = 0.58) of PTX survival (82.7% and 63% at 6 and 60 months, overall). Our data confirm that the MELD score (with only 3 parameters) is as good as the C-Pugh score for predicting mortality on the Eurotransplant waiting list and that the optimal cut-off for assessing higher priority for the bad category is > 16. Contrary to the US data, there was no negative impact on short or long-term PTX prognosis of the bad categories.

HCV GENOTYPE 5 : AN EASY TO TREAT POPULATION. C. Reenaers (1), J. Delwaide (2), C. Gérard (3), B. Bastens (4), C. Bataille (5), F. Boemer (6), B. Servais (7), J. Belaiche (8), +. GLEVHE (9), A. de Roover (10), O. Detry (11), P. Honoré (12), M. Meurisse (13), B. Rentier (14), D. Vaira (15). (1) Gastroentérologie Sart Tilman ; (2) Gastroentérologie Sart Tilman ; (3) Immunohémato Sart Tilman ; (4) St-Joseph Liège ; (5) CHR Huy ; (6) Hôpital Malmédy ; (7) Bois de Abbaye Liège ; (8) Gastroentérologie Sart Tilman ; (9) Groupe Liégeois Etude Virus Hépatotropes ; (10) Chirurgie Sart Tilman ; (11) Chirurgie Sart Tilman ; (12) Chirurgie Sart Tilman ; (13) Chirurgie Sart Tilman ; (14) Virologie Sart Tilman ; (15) Virologie Sart Tilman.

Very little is known about patients infected with HCV genotype 5, due to the low prevalence of this genotype around the world (prevalence of 1.5 % in our area).

Aim of the study : to better define the characteristics of these patients (pts) and to evaluate the answer to therapy.

Methods : the files of 14 pts with genotype 5 were retrospectively reviewed.

Results : Mean age was 42, with 60% female. All patients were of subtype 5a. All were of European origin (Belgium 13, Romania but with contamination in Belgium 1). Most have been contaminated by transfusion (transfusion 11, professional 1, unknown 2). All patients infected by transfusion were contaminated recently, between 86 and 91 (except 1 contaminated in 82). There were no IV drug addicts. A liver biopsy was performed in nine patients : 8 had a fibrosis of F2 ; only one had cirrhosis (patient transfused in 91). Seven patients have received a treatment. One patient treated with interferon (IFN) monotherapy did not respond to therapy. Four patients have been treated with IFN and ribavirin. Three of them (one of whom treated for 6 months) developed a sustained viral response (SVR) (75%) while one, responder during the treatment, had to stop therapy after 4 months due to dysthyroidy. He developed a relapse. Two were treated with PegIFN and ribavirin. One (treated during 6 months) became SVR ; the follow-up results for the second patient (responder after a treatment of 12 months) are pending. The most common reason for considering patients as non eligible for treatment were normal transaminases (4/7 untreated patients).

Conclusions : Patients infected with genotype 5 have been contaminated in Belgium, mostly by transfusion around 1990. Treatment with interferon or peginterferon plus ribavirin seems to give a high rate of SVR (80%).

THE HEP CAR REGISTRY : REPORT ON A ONE-YEAR REGISTRATION PROGRAM OF HEPATO-CELLULAR CARCINOMA IN BELGIUM. H. Van Vlierberghe (1), I. Borbath (2), N. Bourgeois (3), J. Henrion (4), The BASL Steering Committee. (1) Dpt of Gastroenterology, Ghent University Hospital ; (2) Dpt of Gastroenterology, Cliniques St Luc, Brussels ; (3) Dpt of Gastroenterology, ULB Erasme, Brussels ; (4) Dpt of Gastroenterology, Hôpital Jolimont, Haine St Paul.

Introduction : Hepatocellular carcinoma (HCC) is a primary tumour of the liver. Its behaviour is rather peculiar with prognosis made out not only by the tumoural disease but also by the severity of the underlying liver disease. The HepCar registry is an initiative under the auspices of the BASL where patients with HCC are registered.

Methods : After introduction of the initiative during the Winter meeting in December 2002 to the members of the BASL and to the public by the BASL newsletters, physicians were asked to report all new cases of HCC which were seen between January 2003 and December 2003. Reporting was done at a voluntary basis which could have resulted in a recruitment bias. Data were sampled at a central site where collection and statistical work was done. Data reported here are data until the beginning of November 2003.

Results : In this HepCar registry, 70 patients (51 male/19 female) were reported. Median age was 62 years \pm 12. Underlying liver disease was hepatitis C virus related in 29 patients, hepatitis B virus related in 14 patients, alcoholic liver disease in 16 patients and miscellaneous in 12 patients. Cirrhosis was present in 67 out of 70 patients. Diagnosis was made by surveillance in 27 patients. There was a clear tendency for incidental diagnosis in patients with alcoholic liver disease and in younger patients with hepatitis B virus infection. In only a minority of the reported cases, curative treatment (liver transplantation, surgical resection, percutaneous ablation) could be offered.

Discussion : The HepCar registry confirms the abundance of hepatitis C virus infection as an underlying liver disease in the majority of the Belgian HCC patients. Surveillance was reported to be the manner of diagnosis in only a minority of the patients. Alcoholic liver disease and hepatitis B virus infection in a younger population remain two situations where surveillance is not possible or not helpful. Strategies to detect HCC in these two populations should be worked out. Only a minority of the patients could be offered a potential curative treatment. This confirms the dismal prognosis of HCC in the majority of patients living in Belgium.

HEPATITIS C INFECTION : ELIGIBILITY FOR ANTIVIRAL THERAPIES. R. El Saouda (1), J. Delwaide (1), C. Gérard (2), J. Belaiche (1), A. de Roover (3), O. Detry (3), P. Honoré (3), M. Meurisse (3), B. Rentier (4), D. Vaira (4) + GLEVHE (Groupe Liégeois Etude Virus Hépatotropes). (1) Gastroentérologie ; (2) Immunohémato ; (3) Chirurgie ; (4)Virologie, CHU Sart Tilman, Liège.

Current treatments of chronic hepatitis C are effective but expensive. To estimate the global cost of treatment for a country, it is important to evaluate the proportion of patients that are treatment candidates.

Aim of the study : To determine the applicability of antiviral therapy in chronic hepatitis C patients (pts).

Methods : the files of 237 consecutive pts referred for positive PCR-C between 1996 and 2003, when effective therapies were available, were reviewed.

Results : Mean age was 49.2 ± 15.1 , 50.4 % were male. Risk factors were transfusion (43%), IV drug use (23%), needle stick injury (1%), sexual (0.5%), others (32.5%). Genotypes were 1 (66%), 2 (10%), 3 (11.5%), 4 (10.5%), 5 (2%). Were not treated 151 pts (64%). The reasons for not being a treatment candidate were : normal ALT levels (21%), non adherence to evaluation procedures (24.5%) (for example pts who did not attend the appointment for liver biopsy, or who missed more than two office appointments), medical contraindications (34 %). 18% declined therapy despite being considered a treatment candidate. A refusal of reimbursement was the cause of no treatment in 2.5%. The medical contraindications were : psychiatric (29.5%) including poorly controlled severe depression, previous suicide attempt or suicide ideation, ongoing drug or alcohol use, age (25.5%), cirrhotic decompensation (15.5%), willingness of pregnancy (14%), neoplasm (8%), cardiac contraindication (8%), hematological disturbances (4%), and retinopathy (4%). Only 86 pts (36%) were treated. A sustained viral response was obtained in 42 %. The treatment was interrupted in 16% for adverse events.

Conclusions : Only one patient out of three is eventually treated. Only 15% of the whole population of pts referred for chronic hepatitis C becomes sustained responders.

READ BY TITLE

HIGHER MELD SCORES PRE LIVER TRANSPLANTATION HAVE NO INFLUENCE ON THE LONG TERM SURVIVAL OF THE LIVER TRANSPLANT PATIENT. E. Nagler (1), H. Van Vlierberghe (1), R. Troisi (2), I. Colle (1), M. De Vos (1), B. de Hemptinne (2). (1) Dpt of Gastroenterology, Ghent University Hospital ; (2) Dpt of Hepatobiliary Surgery and Liver Transplantation, Ghent University Hospital.

Introduction : Since the implementation of the MELD score in the USA as a score to allocate livers to patients on the liver transplant waiting list, fewer patients died or were removed from this waiting list. Early survival(90 days) showed no difference under the MELD system compared with early survival in the pre-MELD era. However, if the principle 'sickest patient first' could result in a worse long term survival is unknown. We examined the influence of the MELD score on the long term survival of liver transplant patients.

Materials and methods : By a search through the files of Belgian adult patients transplanted for a non fulminant liver failure in the period between January 1991 and December 2001, we included 121 patients. MELD score was calculated as stipulated by Wiesner et al by using variables taken as close as possible prior to liver transplantation. Log rank testing and Kaplan Meier survival curves were performed using different cut off levels for the MELD score (15, 18, 20 and 25).

Results : Indications for transplantation were mainly alcoholic (38 %) or HCV (26.4%). Gender distribution was male : 62 % versus female 38%. Mean age was 54 years \pm 10 years. Mean MELD score was 16 ± 6 . The follow up time was 5.38 years (range : 1.6-12.3 years). By using different MELD cut off levels, no difference in survival at different time points was noted.

Discussion : Using the MELD score as an allocation tool, has no influence on the long term survival of the liver transplant patient. Together with the better selection of the patients on the waiting list, the MELD score seems to be a superior allocation system.

LACK OF EVIDENCE OF SIGNIFICANT EFFECT OF PIRACETAM ON VIROLOGICAL AND BIOLOGICAL RESPONSE IN PATIENTS WITH CHRONIC HEPATITIS C NON RESPONDING TO A PREVIOUS INTERFERON THERAPY. P. Langlet (1), L. Lasser (2), J. Delwaide (3), P. Denis (4), M. Talib (2), M. Dereuck (2), F. Dunham (5), J. Otero (1), P. Marliere (5), J. Nyst (1), C. Jonas (2), E. Dekoster (2). (1) CHIREC and CHU Brugmann, ULB ; (2) CHU Brugmann, VUB-ULB ; (3) CHU Sart Tilman, ULg ; (4) CHU Brugmann, ULB ; (5) CHIREC, ULB.

Introduction : It was suggested in the press* that Piracetam could have anti-viral effect namely against the virus HCV, HBV and HIV. These suggestions were based on conformational studies** showing that Piracetam has properties similar to those of the fusion peptide of viral proteins, interacts with lipids and hereby has beneficial effects on several symptoms of Alzheimer's disease. It was postulated that the potential anti-HCV role could be explained by a stabilization of the lipid membranes of hepatocytes. Early biological and virological effects of Piracetam were investigated in non IFN-responders HCV+ patients (NR).

Methods : 8 NR patients (3F/5H, median age 59 years) were included in this study to receive Piracetam (4.8 g/d) during 3 months. Serum quantitative HCV RNA and ALT level were analyzed at baseline and after 3 months of Piracetam therapy (T-test was used for dependent samples).

Results : 75% pts were infected with genotype 1 (1pt with genotype 3 and one with genotype 4). No side effect was seen during therapy. No significant biological ALT effect ($p=0.88$ NS) and virological effect ($p=0.95$ NS) were observed after 3 months of therapy. 37,5% (3/8 pts) and 0% had a significant increase of respectively ALT level and HCV viral load after 3 months therapy.

Conclusions : No evidence of biological and virological effects of Piracetam in monotherapy were observed in patients with chronic HCV non-responders to a previous IFN-therapy.

* Le Soir, janvier 2003 and TV News-RTBF 1/03

** Biochimica and Biophysica acta 2003 ;1609 :28-38

LIVING RELATED LIVER TRANSPLANTATION IN ADULTS : FIRST YEAR EXPERIENCE AT THE UNIVERSITY OF LIEGE. O. Detry, A. De Roover, J. Delwaide, J. Joris, M. Meurisse, P. Honoré. Dpt of Liver Surgery and Transplantation, CHU Sart Tilman B35, B4000 Liège.

Living related liver transplantation (LRLT) has been recently developed for adult recipients, but puts the donors at risk of serious post-operative complications, or even death. The aim of this paper is to report the prospective evaluation of the first of year experience of adult LRLT at the University of Liège. Between March 2002 and March 2003, in a consecutive series of 35 adult liver transplantations, 5 recipients (mean age : 51 years) underwent LRLT, including one retransplantation. Indications for LT were autoimmune hepatitis, HBV cirrhosis with hepatocarcinoma (2 cases), HCV cirrhosis with hepatocarcinoma, and ischemic intrahepatic bile duct necrosis 10 years after primary LT. Mean age of the donors was 34 years (range : 21-53 years). All cases were intra familial at first degree. The right lobe was used as a graft in four cases and the left lobe in one case. All right lobe donors developed transient hyperbilirubinemia and hypo-coagulation for 4 to 6 days. No severe complication (transfusion, bile duct fistula, reintervention, rehospitalization) was observed in the donors. One donor suffered from bladder retention with secondary E. Coli infection, treated by oral antibiotics. In the recipients, graft function was immediate, and there was no small-for-size syndrome. One patient had biliary fistula treated by reoperation. One recipient died from invasive aspergillosis 11 days after the procedure. The 4 others recipients were alive without recurrence of the disease at follow-up. As a conclusion, LRLT may be an alternative to cadaveric LT in the organ donor shortage era. However risks are real and significant for the donors.

LIVER TRANSPLANTATION IN JEHOVAH'S WITNESSES. O. Detry, A. De Roover, J. Delwaide, P. Damas, A. Kaba, J. Joris, M. Meurisse, P. Honoré. Dpt of Liver Surgery and Transplantation, CHU Sart Tilman B35, Liège, Belgium.

Background : For religious reasons, Jehovah's witnesses (JW) refuse transfusions of any blood product, including autologous or homologous predonated blood, platelets, fresh frozen plasma, coagulation factor concentrates. However they may accept solid organ transplantation. In this paper the authors present their experience of liver transplantation (LT) in JW. Methods : In a 3-year period, 18 JW patients were evaluated for LT. A hematocrit of 40% and a platelet level of 75.000 /mm³ were considered as the minimal acceptable levels for LT. All patients received perioperative iron supplementation and erythropoietin. Two patients had percutaneous spleen embolisation to increase platelet level. High dose aprotinin was given during LT to limit fibrinolysis and meticulous surgical hemostasis was achieved using argon beam coagulation. Continuous circuit cell salvage and reinfusion whereby scavenged blood was maintained in continuity with the patient's circulation, was used. Venovenous bypass was avoided during LT to minimize the coagulation disorders. Two patients received recombinant factor VIIa during liver dissection and at reperfusion.

Results : Five patients were not considered for LT for various reasons. 13 were accepted but 4 died from complications of liver failure while they were in administrative and medical preparation for LT, before being listed. They had been looking for a center accepting to transplant them since more than 6 months and were in Child C when seen in our center. Two did not get approval from their health care system to get LT in the authors' center and were not transplanted in their own country, as they did not find any center agreeing to transplant them. Seven patients were listed for LT and were successfully transplanted. Four of them were in CHILD C. Five received a cadaveric liver graft and 2 a right lobe from a live related donor. All adult patients were treated according to the patients' beliefs. One 6-y-old child received one unit of blood 15 days after LT, because of symptomatic deep anemia secondary to peritonitis due to perforated gastric ulcer. One patient died from aspergillosis and all other patients are alive and well at follow-up.

Conclusion : LT may be successful in carefully prepared JW patients who should not be a priori excluded from this life saving procedure.

A PROSPECTIVE OPEN, SINGLE ARM, PILOT TRIAL TO ASSESS THE SAFETY AND EFFICACY OF ORLISTAT IN OBESE LIVER TRANSPLANT PATIENTS. F. Nevens (1), G. Vandeplas (1), E. Muls (2), M. Roelands (2), C. Verslype (1), R. Aerts (3), J. Fevery (1), J. Pirenne (3). (1) Hepatology ; (2) Endocrinology ; (3) Abdominal Transplantation Surgery, KU Leuven/UZ Gasthuisberg, Leuven.

Background : Obesity an increasingly frequent problem after liver transplantation (LT), decreases patient survival. Orlistat is an approved treatment for obesity but its safety and efficacy in LT has not been explored.

Study population : patients transplanted > 1 y with a BMI > 30, despite an hypocaloric regime for > 6 months ; 20 pts were selected, 19 started. Immunosuppression : tacrolimus or cyclosporine ± azathioprine or mycophenolate. Treatment duration : 6 months 120 mg orlistat tid followed by 120 mg ed during 3 m and further follow up until 12 m. Treatment was interrupted after 3 m if BMI did not change.

Results : Treatment was well tolerated ; adaptation of tacrolimus was necessary in 6/15 pts (dosis reduction in 5 pts) and in 2/4 pts under cyclosporine) ; no biochemical toxicity was observed. 3/19 pts were non responders. Evolution of BMI till end of treatment : 33.8 ± 4.3 to 30.7 ± 4.1 ($p=0.04$) ; 3/16 had rapid weight gain after interruption of treatment ; 13/19 pts had a sustained response : evolution of BMI in this group : t_0 33.5 ± 4.4 , t_{12m} 29.8 ± 3.8 ($p<0.01$) and waist circumference cm : t_0 111.7 ± 11.1 , t_{12m} 96.3 ± 9.5 ($p<0.01$).

Conclusion : Orlistat is safe after LT. Minor dosis adjustments of immunosuppression are required. In 68% a sustained weight loss was observed with a follow-up of 6 months.

MOLECULAR EPIDEMIOLOGY OF HEPATITIS C AMONG DRUG USERS : CORRELATION WITH CLINICAL PARAMETERS, SEXUAL BEHAVIOUR AND DRUG-RELATED RISK BEHAVIOUR. C. Matheï (1), G. Robaey (2), M. Van Ranst (1), P. Van Damme (3), F. Buntinx (1). (1) Katholieke Universiteit Leuven ; (2) Ziekenhuis Oost Limburg ; (3) Universiteit Antwerpen.

Background : The Hepatitis C virus (HCV) is a single stranded RNA virus exhibiting an important genetic diversity. Determining the genotype is crucial for epidemiological as well as for clinical analysis since HCV genotypes differ according to the route of transmission, in geographic distribution and in response to treatment. The objective of this study was to determine the genotypic variation among drug users in 2 regions in Flanders and to relate the genotype distribution to the characteristics of the population.

Methods : HCV-RNA quantification and genotyping was performed on samples from 161 anti-HCV positive drug users. A standardized interview providing information on their socio-demographic status, drug-related and sexual risk behaviour was available for each drug user.

Results : HCV-RNA was present in 152 out of 161 samples. The genotype could be determined for 148 cases. Genotype 1 was predominant (48.6 %), followed by genotype 3 (41.2 %), genotype 4 (8.8 %) and genotype 2 (1.4 %). In the univariate analysis HCV genotype was related to geographic region, history of IDU, number of sexual partners last year, having a tattoo and the presence of anti-HBc. In the multivariate analysis having no history of injecting drug use (IDU) was confirmed as a statistically significant predictor for an infection with genotype 1. Predictors for an infection with genotype 3 were found to be the presence of anti-HBc antibodies and a history of injecting drug use. Being tattooed emerged as a statistically significant predictor for an infection with genotype 4.

Conclusion : The distribution of HCV genotypes in IDU differs significantly from the distribution among non-IDU, genotype 3 being predominant among the former and genotype 1 among the latter. The results of this study are suggestive for a possible role of tattooing practices in the spread of HCV among drug users.

NUTRITIONAL STATUS IN LIVER TRANSPLANT (LTX) CANDIDATES. I. Colle (1), H. Van Vlierberghe (1), L. Vandebussche (1), R. Troisi (2), M. De Vos (1), B. de Hemptinne (2). (1) Dept of Hepato-Gastroenterology, Ghent University Hospital ; (2) Dept of Hepato-biliary Surgery, Ghent University Hospital

Introduction : Chronic liver disease and failure is associated with nutrient deficiencies and malnutrition which lead to an increase in morbidity and mortality before and after transplantation.

Aim of the study : To make an objective evaluation of the nutritional status and the different deficiencies present in patients on the waiting list for LTx and correlate them with the outcome.

Patients and methods : 35 patients (68% men) with chronic liver disease (46% alcoholic ; 14% cholestatic ; 18% adenomatosis and polycystosis ; 22% other causes) on the waiting list for LTx were evaluated for food intake during 3 days (writing method) to have an idea about the energy ; protein ; fat and carbohydrate intake. Anthropometric parameters (triceps skin fold ; arm and arm muscle circumference), BMI and weight loss were evaluated. 15/35 (43%) were transplanted.

Results : The energy intake is 2030+/-540 kcal per day, this is 1124 kcal below the normally advised amount. The minimal advised energy intake is not reached by 92% of the patients. The protein intake is 1,35g/kg body weight (BW) which is 20% of the total energy intake. The carbohydrate intake is too low (48%) but fat intake is normal (32%). The anthropometric results are given in table.

	<percentile 50	<percentile 25	<percentile 5
BMI	68,6%	31,4%	14,3%
Triceps skin fold	71,0%	61,3%	29,0%
Arm circumference	80,6%	71,0%	19,4%
Arm muscle circumference	74,2%	60,0%	22,5%

Hair loss, dry skin, thin nails has been observed in 26%, 66% and 34% respectively. The muscle loss is less important in patients with Child Pugh A class, women and patients with adenomatosis/polycystosis. Patients with good anthropometric results have a shorter stay in the hospital and on ICU than those with malnutrition. However, the patients with the largest food and calorie intake are those with the bad anthropometric results and the longest stay in hospital/ICU. **Conclusion :** The energy intake in patients candidates for LTx is too low and should be increased by a higher intake of carbohydrates, especially polysaccharides. Initially there is more fat catabolism followed in the later stage by muscle catabolism. Patients with a bad nutritional status have the largest energy intake, however, not enough to correct their malnutrition and catabolic status, leading to a longer hospital and ICU stay. An individualised nutritional advice, early in the disease evaluation, is necessary to optimise the food and energy intake.

SYNGENIC FOETAL LIVER IMPLANTATION IN RATS WITH DUCTUS CHOLEDOCUS LIGATURE. V. Coulic (1), C. DePrez (2), P. Delrée (3), B. Sidi (2), E. DeKoster (2). (1) CHU Brugmann, ULB, Brussels ; (2) CHU Brugmann, Brussels ; (3) IGC, Lovreval.

Previous experiments have proved that ectopic development of syngenic foetal liver grafts was possible but limited, maybe due to the absence of functional demand (healthy host). Hence the aim of the present work was to test the possible influence of the host hepatic insufficiency on the evolution of the grafts.

Material and methods : 24 Wistar and Fischer rats were used. All of them underwent ductus choledocus ligature but 12 also received liver implants of foetal liver (donor age : 15-20 days i.u.). The graft sites were a subcutaneous ear pouch (as previously) but also a mesenterium pocket close by the host small bowel. The host functional condition was tested by half quantitative biochemistry of the urine (bilirubin, urobilinogene and protein determination), optic microscopy of the host liver and kidneys. The evolution of the grafts was followed by optic microscopy of biopsies at different times p.o. up to 3 months.

Results : The outcome of the operation of ductus choledocus ligature (DCL) was better in the series with foetal liver implantation (FLI), than in control (2 operative deaths versus 3 ; 3 deaths during the first 3 weeks versus 6, 7 survivals longer 3 weeks versus 3). In the first period after the operation (p.o.), DCL caused acute hepatic and particularly kidney failure. In some cases of survival longer than 1 month, an equilibrium seemed to be reached : liver functional and morphological alterations were moderate. Foetal liver segments implanted in a mesenterium pocket developed the same way as they did in a subcutaneous ear pouch. They underwent a destructive phase more important in the deep layers. The reconstructive phase was observed earlier in the surface layers than in the deep ones. In one case a teratome has developed on the site of intraperitoneal liver implant.

Discussion and conclusion : 1. DCL is a satisfactory model for acute and chronic hepatic alterations, is appropriate to our objectives, though it has certain peculiarities, worth further studies. 2. FLI seems to have a positive influence in early and, especially, in late delays on the survival and the condition of the rats with DCL. 3. Stem cell involvement in foetal liver regeneration is possible as far as teratome growth was observed. The question is : who these cells belong to (host or graft) ? 4. The capacities of host liver adapting to DCL, as well as the role of foetal liver graft in this process, have to be further investigated. 5. Application of FLI for human liver cirrhosis treatment may be suggested but still needs additional animal investigations.

INHIBITORY PATHWAYS IN CIRCULAR MUSCLE OF RAT JEJUNUM. G. Vanneste, R.A. Lefebvre. Heymans Institute of Pharmacology, Ghent University, Ghent, Belgium.

Conflicting literature data have been reported on the contribution of nitric oxide (NO) to inhibitory neurotransmission in rat jejunum. Therefore the mechanism of relaxation of NO and of the other putative neurotransmitters adenosine 5'-triphosphate (ATP), vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase activating peptide (PACAP) was examined in the circular muscle layer of Wistar rat jejunum and their contribution to inhibitory neurotransmission was systematically examined. Mucosa-free circular muscle strips were precontracted with methacholine in the presence of guanethidine and exposed to electrical field stimulation (EFS) and exogenous NO, ATP, VIP and PACAP. All stimuli induced a reduction of tone as well as an inhibition of phasic motility ; this combined response was evaluated by determination of the area under the curve. Only the electrically induced responses were sensitive to tetrodotoxin (3×10^{-6} M). NO (10^{-6} - 10^{-4} M) induced concentration-dependent relaxations that were significantly inhibited by the soluble guanylyl cyclase inhibitor 1H-[1,2,4]-oxadiazolo-[4,3-a]-quinoxalin-1-one (ODQ ; 10^{-5} M) and the small conductance Ca^{2+} -activated K^{+} channel blocker apamin (APA ; 3×10^{-8} M). Relaxations elicited by exogenous ATP (10^{-4} - 10^{-3} M) were significantly inhibited by the P2Y purinoceptor antagonist Reactive Blue 2 (RB2 ; 3×10^{-4} M) but not by APA and ODQ. The inhibitory responses evoked by the peptides VIP (10^{-7} M) and PACAP (3×10^{-8} M) were significantly decreased by the selective PAC1 receptor antagonist PACAP₆₋₃₈ (3×10^{-6} M), APA and RB2. The selective VPAC2 receptor antagonist PG 99-465 (3×10^{-7} M) reduced the relaxations caused by VIP but not those by PACAP, while the selective VPAC1 receptor antagonist PG 97-269 (3×10^{-7} M) had no influence. Relaxations induced by EFS (40V, 0.1 ms, 1-8 Hz for 20 sec) were significantly inhibited by the NO-synthase inhibitor N^w-nitro-L-arginine methyl ester (L-NAME ; 3×10^{-4} M), ODQ and APA, but not by RB2, PG 97-269, PG 99-465 and PACAP₆₋₃₈. These results suggest that NO is the main inhibitory neurotransmitter in circular muscle of Wistar rat jejunum and that the followed pathway involves a rise in cGMP levels and the activation of SK K^{+} channels.

INFLUENCE OF VAGOTOMY ON 5-HT₁ AND 5-HT₇ RECEPTOR MEDIATED STOMACH RELAXATION IN CONSCIOUS DOGS. P. Janssen (1), N. Prins (2), B. Moreaux (2), A. Meulemans (2), R. Lefebvre (5). (1)Heymans Institute of Pharmacology, Ghent University, Ghent, Belgium ; Johnson & Johnson Pharmaceutical Research and Development, Beerse, Belgium ; (2) Johnson & Johnson Pharmaceutical Research and Development, Beerse, Belgium ; (5) Heymans Institute of Pharmacology, Ghent University, Ghent, Belgium.

We previously showed that the 5-HT_{1A} receptor agonist flesinoxan and the 5-HT_{1/7} receptor agonist 5'-carboxamidotryptamine (5-CT) induced canine gastric relaxation *in vivo*. The influence of vagotomy on their gastric relaxant effect was now investigated to assess whether vagal mechanisms are involved. Beagle dogs were equipped with a gastric fistula. Volume changes within an intragastric bag were measured in the conscious state by means of a barostat. Results are presented as mean±SEM ; n=5-11. Both flesinoxan (10-150 µg/kg) and 5-CT (0.5-10 µg/kg) induced a dose-dependent gastric volume increase (50±10 - 275±33 ml for flesinoxan and 24±10 - 267±36 for 5-CT). This relaxation was dose-dependently inhibited by the selective 5-HT_{1A} receptor antagonist WAY-100635 (0.5-30 µg/kg) and the selective 5'-HT₇ receptor antagonist SB-269970 (5-50 µg/kg) respectively. N^G-nitro-L-arginine methyl ester did not influence the effect of flesinoxan and 5-CT. After supradiaphragmatic vagotomy, experiments were performed under bethanechol infusion to compensate for the loss in vagal cholinergic input to the stomach. Flesinoxan was no longer able to relax the stomach after vagotomy while 5-CT still induced a gastric relaxation.

It is concluded that 5-CT induces gastric relaxation in conscious dogs via peripherally located 5-HT₇ receptors. The gastric relaxant effect of flesinoxan is mediated through a vagal pathway ; the actual results do not allow concluding whether flesinoxan interacts with the vagal nerves at a central or peripheral level. Neither 5-CT- nor flesinoxan-induced stomach relaxation involves activation of nitrergic pathways.

5HT₃ AGONISTS INDUCE FUNDIC RELAXATION BY ACTIVATION OF 5-HT₃ RECEPTORS IN THE DUODENAL WALL. P. Claes, K. Smans, E. Ghoois, A. Wellens, L. Ver Donck, J. Schuurkes. GI Pharmacology, Janssen Pharmaceutica, Beerse.

In this report, we demonstrate that activation of 5-HT₃ receptors on the duodenal wall induces fundic relaxation in the fasted conscious dog. Since fundic accommodation is impaired in patients with functional dyspepsia, this finding could lead to a new approach in the treatment of this disorder. Experiments with the barostat technique showed that intraduodenal (ID) administration of m-chlorophenylbiguanide (CPB) or 2-methylserotonin (2Me5-HT), two selective 5-HT_{3R} agonists, results in a dose-dependent fundic relaxation. Intravenous (IV) injection of 5-HT_{3R} agonists results in a pronounced tachycardia, and was therefore not further tested. Granisetron, a 5-HT_{3R} antagonist, potently blocks the relaxing effect. Furthermore, granisetron is more efficient when administered ID than IV. Moreover, local anaesthesia of the duodenal mucosa inhibits the effect of the agonists significantly. Immunohistochemical microscopy with an anti-5HT_{3R} antibody revealed that 5HT_{3R}- containing nerve axons penetrate into the duodenal mucosa. The receptors therefore could well be accessible by lumenally applied 5-HT_{3R} agonists. In conclusion, we demonstrate that 5-HT₃ receptor agonists induce a fundic relaxation in the fasted conscious dog when administered intraduodenally. This mechanism appears to involve 5-HT₃ receptors on extrinsic afferent nerve-endings situated in the duodenal wall.

EFFECTS OF ACUTE INTRAVENOUS ADMINISTRATION OF CITALOPRAM ON GASTRIC SENSORIMOTOR FUNCTION IN MAN. C. Casteels (1), L. Van Oudenhove (2), R. Vos (1), J. Janssens (1), J. Tack (1). (1) Center for Gastroenterological Research. K.U. Leuven. Belgium ; (2) Liaisonpsychiatrie K.U. Leuven. Belgium.

Studies in animals have shown involvement of serotonin (5-HT) in the control of the gastric accommodation reflex. Selective 5-HT reuptake inhibitors (SSRIs) enhance the availability of synaptically released 5-HT during short term treatment and desensitise 5-HT receptors during prolonged treatment. In a recent study in man, 5 days pre-treatment with the selective SSRI paroxetine was shown to enhance gastric accommodation, but it is unclear whether this reflects enhanced availability of 5-HT or receptor desensitisation.

Aim : The present study was to assess the effects of acute i.v. administration of the SSRI citalopram on gastric sensorimotor function in man.

Methods : Nine healthy subjects (5 men, mean age 23 ± 1) underwent a gastric barostat study twice with at least a week interval. After introduction of a flaccid barostat bag in the stomach and a recovery period, the pressure level was set at intra-abdominal pressure (MDP)+ 2 mm Hg 50 min. before and until recovery to baseline after administration of a standardized meal. After 30 min., saline or citalopram was administered i.v. over 20 min in a double-blind randomised cross-over fashion. Subsequently a liquid meal (200 ml ; 300 kcal) was administered and measurement continued for another 60 min.

Results : Baseline intra-balloon volumes were comparable between both groups. Mean pre-prandial intra-balloon volumes were similar after saline or citalopram (231 ± 32 vs. 273 ± 40 ml, NS), although a transient relaxation was seen during citalopram infusion, with a peak of 342 ± 62 ml at 15 min. Mean postprandial volumes did not differ significantly after saline or citalopram (respectively 439 ± 42 and 363 ± 41 ml, NS), but postprandial volumes after citalopram were significantly lower than those after saline (ANOVA, $p<0.0001$). The average increase of intra-balloon volume during the 30 minutes and 60 minutes postprandial period tended to be smaller after citalopram (respectively 224 ± 36 vs. 93 ± 73 , $p=0.05$ and 218 ± 36 vs. 84 ± 79 ml, $p=0.06$). The maximal postprandial increase in intra-balloon volume (305 ± 38 vs. 215 ± 67 , NS) and the time to maximal postprandial volume (19 ± 4 vs. 23 ± 6 min, NS) and the duration of the meal-induced relaxation (87 ± 8 vs. 73 ± 10 min) were not affected by citalopram.

Conclusions : Acute i.v. administration of the SSRI citalopram inhibits gastric accommodation to a meal in healthy subjects. Further studies will be required to elucidate the role of 5-HT in the control of the accommodation reflex.

INFLUENCE OF FEARFUL MOOD AND EMOTIONAL CONTEXT ON GASTRIC SENSORIMOTOR FUNCTION IN MAN. B. Geeraerts (1), J. Vandenberghe (1), L. Van Oudenhove (1), L.J. Gregory (2), Q. Aziz (2), P. Persoons (1), J. Janssens (1), J. Tack (1). (1) Center for Gastroenterological Research, K.U.Leuven, Belgium ; (2) Section of GI Sciences, University of Manchester, Manchester, UK.

Previous research in functional dyspepsia showed an association between gastric hypersensitivity and psychopathological dimensions such as anxiety. It is unclear whether a causal relationship exists between both, or whether anxiety and visceral hypersensitivity share a common predisposition.

Aim : the present study was to investigate whether mood induction within an emotional context of anxiety would alter gastric sensorimotor function in healthy controls.

Methods : Mood and emotional context were induced by means of simultaneous visual projection of standardized validated facial expressions (neutral/fearful) and an audio-tape recalling a neutral or fearful autobiographical experience. All experiments were performed twice, in a randomized cross-over fashion, and anxiety was assessed on visual analogue scale (VAS). Eight healthy subjects underwent a barostat study to assess sensitivity to distention and meal accommodation. Eighteen healthy subjects underwent a 10-minute satiety drinking test (30 ml/min, 1.5 kcal/ml) with registration of intensity of epigastric symptoms on VAS at 2-minute intervals. Mood-induction stimuli were applied during 10 minutes at the start of each measurement.

Results : During a fearful context, gastric compliance was significantly decreased (55 ± 7 vs. 37 ± 8 ml/mm Hg, $p=0.03$) but perception and discomfort thresholds were not significantly altered. During a fearful context, initial gastric accommodation to a meal was inhibited during first 10 (139 ± 25 vs. 53 ± 27 ml, $p=0.03$) or first 30 min postprandially (138 ± 37 vs. 71 ± 30 , $p<0.05$). VAS scores for anxiety confirmed efficacy of mood induction (AUC 9 ± 5 vs. 41 ± 15 mm*min, $p<0.05$). During the satiety drinking test, fearful context was associated with significantly (all $p<0.05$) higher scores for satiety (47 ± 8 vs. 61 ± 3), fullness (44 ± 8 vs. 56 ± 6) and bloating (27 ± 6 vs. 39 ± 6) but not for pain, discomfort, nausea, belching or heartburn.

Conclusion : A fearful mood and emotional context decreases gastric compliance, inhibits meal-induced accommodation and increases perception of early satiety, fullness and bloating after a standardized meal. These observations demonstrate the potential for psychopathological factors to be a causal factor in the pathogenesis of functional dyspepsia symptoms and mechanisms.

INVITED LECTURE

ADVANCES IN ENTERIC NEUROMUSCULAR DISORDERS : FROM BENCH TO BEDSIDE. R. De Giorgio, G. Barbara, V. Stanghellini, R. Cogliandro, F. De Ponti*, M. Tonini** & R. Corinaldesi. Department of Internal Medicine & Gastroenterology and *Department of Pharmacology, University of Bologna ; **Department of Physiological and Pharmacological Sciences, University of Pavia, Italy.

The term "enteric neuropathies" encompasses a spectrum of diseases characterized by a progressive impairment of the morpho-functional integrity of the enteric nervous system (ENS), interstitial cells of Cajal and muscular layer usually associated with severe gut dysmotility. With concern to enteric neuropathies, these are usually secondary to a wide array of systemic diseases, although other cases are idiopathic in origin. This latter group can be further classified into inflammatory and degenerative/non-inflammatory forms. Inflammatory neuropathies are characterized by a dense inflammatory infiltrate confined to enteric plexuses which indicates that inflammation/immune activation could be involved in enteric neuron degeneration. Evidence that patients with inflammatory neuropathies have circulating anti-neuronal auto-antibodies further supports the role of the immune system. Specifically, a subclass of circulating anti-neuronal antibodies (i.e., anti-Hu or ANNA-1) was found to evoke apoptosis via the activation of the two pro-apoptotic molecules Caspase-3 and APAF-1 in isolated primary cultures of enteric neurons. The etiology of inflammatory neuropathies remains undetermined. Degenerative/non-inflammatory forms, either familial or sporadic, are the end result of mechanisms leading to neuronal death. Neuropathological findings include a variety of abnormalities ranging from qualitative to quantitative ENS changes. Although the genes responsible for familial neuropathies are still unknown, recent data mapped the disease locus to chromosome Xq28 region. The mechanisms through which noxious factors initiate degenerative processes in sporadic neuropathies remain obscure. Recent results demonstrated a reduced expression of BCL-2 (one of the major proteins involved in cell survival) and increased apoptosis (identified by TUNEL technique) in the ENS of patients with severe gut dysmotility. In conclusion, these data prompt research efforts provide a basis to better understand the mechanisms underlying enteric neuromyopathies and develop targeted therapeutic strategies for these diseases. *Supported by MURST & a Janssen Pharmaceutical Educational Grant.*

BI-DIRECTIONAL INTERACTION BETWEEN MUCOSAL MAST CELLS AND CGRP-IR EXTRINSIC PRIMARY AFFERENT NEURONS. F. De Jonge (1), A. Kroese (2), A. De Laet (3), L. Van Nassauw (4), H. Miller (5), P. Van Bogaert (6), J. Timmermans (7). (1) Biomedical Sciences, UAntwerp ; (2) Medical Physiology, UMC, Utrecht ; (3) Biomedical Sciences, UAntwerp ; (4) Biomedical Sciences, UAntwerp ; (5) Veterinary Clinical Studies, University of Edinburgh ; (6) Biomedical Sciences, UAntwerp ; (7) Biomedical Sciences, UAntwerp.

Communication between neurites and mast cells is a prototypic example of neuro-immune interaction. We previously reported a close apposition between mucosal mast cells (MMC) and a dense network of calcitonin gene related peptide (CGRP)-IR extrinsic primary afferent nerve fibres in the lamina propria of *S. mansoni*-infected murine ileum (De Jonge et al., 2003). These CGRP-IR fibres originate from dorsal root ganglia (DRG). Using optical recordings of intracellular calcium ($[Ca^{2+}]_i$) we examined the bidirectional interaction between primary cultured MMCs and DRG neurons *in vitro*. The degranulatory EC_{50} for the mast cell degranulator C48/80 (10 μ g/ml) and the neuropeptides CGRP (2.10⁻⁸ M) and SP (3.10⁻⁸ M) were determined by measurement of extracellular mMCP-1. Application of the mast cell degranulator C48/80 (10 μ g/ml) to fluo-4 loaded (1 μ M, 40min, 20°C) MMCs induced a transient rise in $[Ca^{2+}]_i$ in 56 \pm 1% (mean \pm SD ; 3 cultures) of the 260 cells studied, with a lag time of 47 \pm 21s and an amplitude of 7 \pm 2 RF (Relative Fluorescence ; baseline RF=1). A smaller (P<0.01) percentage of MMCs was activated by 10⁻⁷M CGRP (15 \pm 6% ; 3 cultures ; 599 cells) and 10⁻⁷M SP (12 \pm 3% ; 2 cultures ; 547 cells). The lag time of the response to CGRP (33 \pm 26s) and SP (21 \pm 16s) was shorter (P<0.001) than that to C48/80. The CGRP response could be completely blocked by pertussis toxin (2 μ g/ml ; 3h), indicating involvement of G-proteins. Application of 'MMC juice' to fluo-4 loaded DRG neurons (5 cultures) induced a rise in $[Ca^{2+}]_i$, with a lag time of 5 \pm 2s and an amplitude of 2 \pm 0.4 RF. We also showed that degranulation of MMCs by C48/80 in culture dishes containing DRG neurons, caused a comparable activation (1.7 \pm 0.4 RF) of DRG neurons, but with a much longer lag time (25 \pm 10s, P<0.001 ; 2 cultures). In conclusion, these results demonstrate that a bidirectional cross-talk between cultured MMCs and DRG neurons *in vitro*, indicating a functional relevance for the close apposition of MMCs and CGRP-IR nerve fibres *in vivo*. *Supported by IUAP P5/20, FWO-grant G.0377.04 and an IWT-grant (SB1146 to FDJ).*

STUDY OF THE GASTRIC AND INTESTINAL SMOOTH MUSCLE CONTRACTILITY DURING ACUTE NECROTISING PANCREATITIS IN MICE. T.C Seerden (1), J.G De Man (1), B.Y De Winter (1), A.G Herman (2), P.A Pelckmans (1). University of Antwerp - (1) Division of Gastroenterology ; (2) Division of Pharmacology.

Aim : Acute pancreatitis is often associated with gastrointestinal motility disturbances. However, the underlying mechanisms remain largely unknown. We therefore studied the effect of acute necrotising pancreatitis on the contractility of isolated muscle strips from the gastric fundus and jejunum.

Methods : Acute necrotising pancreatitis was induced by feeding young female mice a choline-deficient (CD) ethionine (0.5%) supplemented diet (CDE) for 72 hours. Longitudinal muscle strips were prepared from the gastric fundus and jejunum and mounted in organ baths for isometric tension recordings. Enteric nerve-mediated contractions to electrical field stimulation (EFS, 0.5-8 Hz) and contractions to carbachol (Cch, 10^{-9} - 10^{-6}), substance P (SP, 10^{-9} - 10^{-7}), serotonin (5HT, 10^{-8} - 10^{-5}), prostaglandine F_{2α} (PGF_{2α}, 10^{-8} - 10^{-6}) and KCl 50 mM were studied in control, CD and CDE mice. The severity of the acute pancreatitis was assessed by histological examination. Only mice with a histological severity score ≥ 4 after the CDE diet were included in the CDE group.

Results : EFS, Cch, SP, 5HT, PGF_{2α} and KCl induced contractions in jejunal and gastric fundus muscle strips from control, CD and CDE mice. However, all jejunal contractions were significantly decreased in CDE mice with acute pancreatitis (Table 1), whereas jejunal contractility in CD mice was comparable to control mice (Table 1). On the other hand, acute pancreatitis did not affect the contractility of gastric fundus muscle strips since contractions to EFS, Cch, SP, PGF_{2α} and KCl in the gastric fundus were similar in control, CD and CDE mice.

Conclusion : Acute necrotising pancreatitis leads to a decreased contractility of the jejunum while the contractility of the gastric fundus remains normal during pancreatitis. These results suggest that acute necrotising pancreatitis leads to a disturbed contractile activity of specific regions of the gut.

	EFS 8 Hz	Cch 10^{-6}	PGF _{2α} 10^{-6}	SP 10^{-7}	5HT 10^{-6}	KCl 50 mM
control (n=12)	4.63 ±0.35	7.96±0.51	5.29±0.40	4.36±0.47	6.82±0.49	8.27±0.53
CDE-pancreatitis (n=8)	2.44±0.29*	5.79±0.55*	3.23±0.33*	2.70±0.27*	2.44±0.28*	5.96±0.37*
CD (n=6)	3.79±0.54	8.93±0.80	5.47±0.55	5.22±0.46	5.78±0.61	8.48±0.54

* P < 0.05 compared to mice receiving the control diet for 72 hours (One-way ANOVA, Dunnet post hoc).

MOLECULAR DISSECTION OF VISCERAL SENSATION : EXPRESSION PROFILES OF VAGAL AND SPLANCHNIC AFFERENT NEURONS. PJ. Peeters (1), R. de Hoogt (1), J. Aerssens (1), K. Hillsley (2), A. Stanisz (2), D. Grundy (2), RH. Stead (2), A. Meulemans (1), B. Coulie (1). (1) Johnson & Johnson Pharmaceutical Research and Development ; (2) Holburn Group of Companies.

Background : Vagal afferent neurons are thought to convey primarily physiological information, whereas spinal afferents transmit noxious signals from the viscera to the central nervous system. In order to identify molecular triggers underlying these different properties we compared gene expression profiles of neurons located in nodose (NG) and dorsal root ganglia (DRG) in mice.

Methods : Intraperitoneal administration of Cholera toxin B-Alexa Fluor-488 in 5 mice allowed identification of neurons projecting to the gut. Fluorescent neurons in DRG (from T10 to T13) and NG were isolated using laser capture microdissection followed by extraction, linear amplification and biotin labelling of RNA. Labelled RNA was hybridised to Affymetrix murine arrays, containing probes interrogating expression levels of 12,000 mouse genes. Expression profiles were analysed by applying multivariate spectral map analysis and SAM algorithm (Significance Analysis of Microarray data). Significant differentially expressed genes were defined as follows : at least 1.5 fold difference in expression level, q-value (false discovery rate) below 10% and positioning at the extremities of the spectral map.

Results : In total 918 genes fulfilled the above criteria, including 22 G-protein coupled receptors and 32 ion channels. Important players in visceral sensory processes include serotonin (5-HT), cholecystokinin (CCK), prostaglandin and tachykinin receptors. Eleven 5-HT receptors are represented on the array, of which 6 were reliably detected above background. In agreement with pharmacological and immunohistochemical data, 5-HT_{3A} was 9 times more abundant in neurons derived from NG compared to DRG. In contrast, 5-HT_{5B} was 2 times more abundant in DRG. No differences were found for 5-HT_{5A} and 5-HT₄. Also consistent with literature was the predominant vagal expression of CCK-A receptor whereas CCK-B receptor was equally present in DRG and NG. Similar consistent findings were obtained for prostaglandin E receptors with EP₃ present both in NG and DRG, whereas EP₁ was restricted to DRG. Interestingly EP₄ was more confined to NG. Striking were expression patterns of glutamate receptor 5, substance P, CRF₂ and neurotensin receptor 2. Whereas mRNA levels of the first two were respectively 30 and 10 times higher in DRG, the latter two were mostly restricted to NG.

Conclusion : Gene expression profiling revealed previously unrecognised players contributing to differences between NG and DRG sensory neurons.

EFFECT OF REPEATED INDUCTION OF EXPERIMENTAL ESOPHAGITIS ON ESOPHAGEAL PERISTALSIS, TONE AND SHORTENING. X. Zhang, J. Tack, J. Janssens, D. Sifrim. Center for Gastroenterological Research, K.U.Leuven, Belgium.

Esophagitis is associated with motor abnormalities both in the esophageal body and LES. Reflux disease involves repeated episodes of mucosal inflammation and spontaneous or treatment-induced healing.

Aims : this study was a) to follow up changes in esophageal peristalsis, tone and length induced by experimental acute esophagitis until healing ; and b) to assess the effect of repeated sequences of esophagitis-healing on these motor parameters.

Methods : Experiments were performed on 6 cats. We performed esophageal endoscopy, manometry and barostat before, at 24hs and every 7 days after intraesophageal acid perfusion (0.1N HCl, 80min). Esophageal length was measured during manometry as the distance between lower and upper esophageal sphincters. Esophageal compliance was calculated using stepwise distensions with the barostat. Identical protocol was performed 2 and 4 months after the first acid perfusion.

Results : Acid perfusion induced severe esophagitis (circumferential confluent erosions). At 24hs, distal peristaltic contractions disappeared in 4 cats and had reduced amplitude in 2 cats. LES pressure was reduced by 60%. Esophageal length was 1-2 cm shorter in all the cats and esophageal compliance was reduced by 30%. All these parameters recovered in 4 weeks except compliance that remained low at 8 weeks in spite of mucosal healing. Although the second and third acid perfusions induced similar severe esophagitis the motor effects were milder. With healing after the last perfusion there were no remnant motor changes.

Conclusions : Acute experimental esophagitis provoked decreased phasic contractions and LES pressure, esophageal shortening and increased esophageal tone. In the absence of a new injury, all these changes were reversible. Spaced repeated injuries induced milder motor effects suggesting an adaptive response to the inflammatory factors involved in esophagitis.

	Amplitude (mmHg)	Compliance (ml/mmHg)	Length (cm)	LESP (mmHg)
reduction 24hs after 1st HCL perfusion	146±20 to 10±7*	0.58±0.03 to 0.41±0.07*	17.2±0.5 to 15.8±0.6*	62±16 to 16±5*
reduction 24hs after 2nd HCL perfusion	131±13 to 111±27	0.46±0.05 to 0.43±0.03	17.2±0.5 to 16.5±0.3	48±4 to 44±8
reduction 24hs after 3rd HCL perfusion	128±17 to 79±20	0.55±0.05 to 0.49±0.04	16.8±0.3 to 16.2±0.4*	62±7 to 31±3*

* p < 0.05, paired t test.

INVITED LECTURE

NEW TECHNIQUES AND INSIGHTS IN THE STUDY OF SMALL INTESTINAL MOTILITY. Wim J E P Lammers. Al Ain, United Arab Emirates, Department of Physiology, Faculty of Medicine and Health Sciences, United Arab Emirates University.

Two new technologies in the study of intestinal motility will be presented ; high-resolution electrical mapping and high-resolution motility mapping. High-resolution electrical mapping consists of recording from a large number of closely spaced electrodes and reconstructing the patterns of conduction of slow waves and spikes. In our studies, we have used 240 recording electrodes, both in vitro- and in vivo. Recently, in the anaesthetized dog in vivo, we have shown the occurrence of peripheral slow wave pacemakers and retrograde propagation in the small intestine. Analysis of spikes has shown that spikes conduct in limited areas or 'patches' and that there are two types of patches in the canine small intestine. High-resolution motility mapping consists of digital video recording of the motility of the border of the intestines or of markers located on the serosa. For example, this technique has shown that the direction of the pendular contraction is determined by the direction of propagation of the preceding slow wave.

In conclusion, simultaneous high resolution electrical and motility analysis may provide for a better understanding of the complex patterns of gut motility.

Lammers WJEP, Ver Donck L, Schuurkes JAJ, Stephen B. Longitudinal and circumferential spike patches in the canine small intestine in vivo. Am J Physiol 285, G1014-G1027, 2003.

Lammers WJEP, Dhanasekaran S, Slack JR, Stephen B. Two dimensional high resolution motility mapping. Methodology and initial results. Neurogastroenterology & Motility 13, 309-323, 2001

MAPPING OF SLOW WAVE ACTIVITY IN THE SMALL INTESTINE OF CONSCIOUS DOGS. L. Ver Donck (1), W. Lammers (2), J. Schuurkes (1). (1) Dept. GI-Pharmacology, Johnson&Johnson Pharmaceutical Research and Development, a division of Janssen Pharmaceutica NV, Beerse, Belgium ; (2) Dept. Physiology, Faculty of Medicine & Health Sciences, Al Ain, UAE.

Slow wave (SW) characteristics in isolated tissues and in anaesthetised animals have previously been described. The objective was to map SW propagation in the small intestine of conscious dogs using implanted extracellular electrodes. Electrode arrays were constructed by positioning pseudo-unipolar silver electrodes through a 12×14 mm silicone sheet. Each silicone sheet had 2 rows of 3 electrodes each (4 mm distance from each other). Connecting wires were soldered to each electrode and a second silicone layer was glued on top of the first layer. A silver ring around the wiring of each array served as the reference pole. A row of 4 arrays (4×6=24 electrodes) was implanted on the small intestine (n=4 dogs), covering an intestinal area of ca. 4×55 mm. The wiring was tunnelled subcutaneously to the neck, where they were exteriorised between the scapulae to a connector. Signals were recorded using a National Instruments SCXI (32 channels, bandwidth 2-400 Hz, 1 KHz sample freq.) and displayed using customized LabView software. There were no clinical abnormalities during a 14 month post-operative follow up, indicating preservation of normal intestinal function. No histological changes were observed in the gut wall 2 months after implantation. Electrograms could be recorded from the small intestine for at least 14 months after implantation. SW frequency in the duodenum of conscious dogs was 19.3 ± 2.4 cycles/min (mean±SD) and conduction velocity was 7.5 ± 1.9 cm/sec. Mapping of individual SW's over the 24 electrode array revealed consistent aboral propagation. Spike activity could be regularly recorded and identified. Spike frequency and incidence was increased during MMC-activity, or upon administration of prucalopride (0.31 mg/kg, SC). In conclusion, this implantation technique makes it possible to reliably analyse propagation patterns of individual SW's in conscious dogs for prolonged periods and could provide new insight into the behaviour of the SW as a major determinant of small intestinal motility.

SCHISTOSOMIASIS : IS THE DISTRIBUTION OF INTERSTITIAL CELLS OF CAJAL (ICC) DIFFERENT FROM HEALTHY ILEUM ? S. Chatterjee (1), G. Vrolix (1), E. Van Marck (1), J. Vanderwinden (2). (1) Pathology Unit, Campus Drie Eiken, University of Antwerp ; (2) Neurophysiology Unit, Campus Erasme, Free University of Brussels.

The interstitial cells of Cajal (ICC) generate the pacemaking electrical slow waves of the GI tract and function as a relay between nerves and smooth muscle cells. A complete loss of ICC-deep muscular plexus in the jejunum concomitant with alterations in GI motility was observed in the rat during inflammation induced by *Nippostrongylus brasiliensis* (Faussone-Pellegrini et al. (2002) Neurogastro. Motil. 14 : 83-95). Here we investigated whether the ICC were similarly affected during acute and chronic *Schistosoma mansoni* infections, and thereby may be involved in the disturbed GI motility patterns caused by schistosomiasis. Immunohistochemistry was performed on whole-mounts and cryosections from uninfected, and 8 and 15 weeks *S. mansoni* infected mice ileum. Primary antibodies used were : KIT (the marker for ICC), the neuronal markers VACHT (vesicular acetylcholine transporter), SNAP-25 (presynaptic marker for secretory granules), PGP-9.5 (protein gene product), SK3 (the marker for KIT-negative fibroblast like cells, FLC), and the gap junction protein connexin 43 (Cx43). The secondary antibodies used were donkey anti-goat and donkey anti-rabbit coupled either to FITC or Texas Red. Single and double immunofluorescence staining was performed and analyzed by confocal microscopy. As reported previously, muscle thickness and inflammatory infiltrate increased over time during *S. mansoni* infection. The distribution of the neuronal markers and of Cx43 in the circular muscle layer was unaltered. Apparently normal Kit-ir ICC and SK3-ir FLC were observed at all locations as seen in uninfected controls, and at acute (8 weeks) and chronic (15 weeks) stages of *S. mansoni* infection. A preferential, though not exclusive proximity was noticed between inflammatory infiltrates and SK3-ir FLC, in the muscle layers. In contrast to the loss of ICC reported in the *N. brasiliensis* model of inflammation, all populations of ICC remain present during acute and chronic *S. mansoni* infection, suggesting that the alterations of digestive motility in *S. mansoni* infection are not related to the destruction of some population of cells in the muscularis propria.

IL-1B ACTIVATES MYENTERIC ICCS IN THE GUINEA-PIG COLON. A. Kroese (1), F. De Jonge (2), J. Timmermans (3). (1) Medical Physiology, UMC, Utrecht ; (2) Biomedical Sciences, UA, Antwerp ; (3) Biomedical Sciences, UA, Antwerp.

Myenteric interstitial cells of Cajal (ICCs) are considered to be pacemaker cells for contractile activity in the gastrointestinal tract. Ca^{2+} oscillations observed in ICCs are linked to this pacemaker activity. To determine if ICCs are involved in neuro-immune interactions, effects of the proinflammatory mediator interleukin-1b (IL-1b) on ICCs were investigated in conventional myenteric plexus preparations loaded with Fluo-4-AM (1 mM ; 40 min ; 20°C). The cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$) was measured (at 20°C) by confocal laser scanning microscopy. ICCs, within their network, were recognized by their shape and their lack of response to 75 mM KCl^3 , and were identified afterwards by c-Kit immunohistochemistry. All ICCs (98/104) responded to IL-1b (10 s application) with an immediate (delay < 1 s), fast and transient rise in $[Ca^{2+}]_i$. Application of 4 nM IL-1 β evoked an increase in $[Ca^{2+}]_i$ from 1 (baseline) to 3.4 ± 0.48 RF (Relative Fluorescence ; mean \pm SD ; n=98). The dose-response relation (40 fM to 4 nM) revealed an EC_{50} of IL-1 β of approximately 50 pM. The responses of 14 ICCs (14/98) showed $[Ca^{2+}]_i$ oscillations whose frequency of about 0.3 Hz is comparable to that of spontaneous $[Ca^{2+}]_i$ oscillations reported in cultured ICCs. Continuous perfusion with IL-1 β (80-400 pM ; 60 min ; n=8 ; 21 ICCs) evoked a long-term increase in $[Ca^{2+}]_i$. The responses of ICCs to IL-1 β were reproducible and reversible and were not affected by blockade of prostaglandin synthase (Indomethacine 1 μ M ; 7 expts ; n=37 ICCs), of neural action potential firing (TTX 1 μ M ; 4 expts ; n=20) or of NO synthase (L-NNA 1 mM ; 2 expts ; n=16). Double immunostainings on intestinal whole mounts with antibodies against c-Kit unambiguously showed the presence of the IL-1 receptor on the cell membrane of myenteric ICCs. In conclusion, these results demonstrate that IL-1 β has a marked, direct excitatory effect on ICCs in the myenteric plexus, indicating that these ICCs may be involved in the neuro-immune regulation of gastrointestinal motility. *Supported by IUAP P5/20 and FWO-grant G.0377.04*

EXPRESSION OF THE $Na^+-K^+-2Cl^-$ COTRANSPORTER, NKCC1, BY MYENTERIC INTERSTITIAL CELLS OF CAJAL IN THE JEJUNUM. M. Wouters (1), K. Smans (1), A. De Kerchove d'Exaerde (2), J. Vanderwinden (2). (1) Dept. Gastro-intestinal Pharmacology, J&J Pharmaceutical Research and Development, a division of Janssen Pharmaceutica ; (2) Labo. Neurophysiology, Université Libre de Bruxelles.

Introduction : Interstitial cells of Cajal (ICC) are important for the generation of pacemaker currents and thus for proper transit along the GI tract. *WlacZ/Wv* and *Sl/Sld* mice, which are deficient in ICC and in slow wave activity, provide valuable models in the quest for ICC specific genes.

Methods : The pool of genes expressed in the muscle coats of the mouse intestine in controls and ICC deficient littermates was compared by Suppression Subtractive Hybridization (SSH) and confirmed by Real Time Quantitative PCR (RT-QPCR). The distribution of the $Na^+-K^+-2Cl^-$ cotransporter (NKCC1) was studied using Immunohistochemistry (IHC). The involvement of NKCC1 in slow wave generation is examined by the s.c. administration of a NKCC1 antagonist, bumetanide, in one dog (0,5 mg/kg).

Results : SSH identified 52 out of 4000 candidate genes putatively downregulated in both the *W/Wv* and *Sl/Sld* ICC-deficient models versus WT animals. Among these 52 genes, *KIT* and *Slc12a2*, which encodes the $Na^+-K^+-2Cl^-$ cotransporter NKCC1, were confirmed to be downregulated by RT-QPCR. *c-Kit* and NKCC1 were respectively $5,3 \pm 0,3$ and $3,5 \pm 0,18$ (n=6) times more expressed in WT than in *Sl/Sld*. In mouse and human jejunum, NKCC1 immunoreactivity was found in the epithelium lining the mucosal crypts, in enteric neurons and in the pacemaking myenteric ICC but not in ICC at the deep muscular plexus. After the s.c. administration of bumetanide in one dog (0,5 mg/kg) no effect could be recorded on the slow wave amplitude or frequency.

Conclusion : NKCC1 and *KIT* were picked up by SSH and confirmed with RT-QPCR. IHC revealed expression of NKCC1 in ICC-MYP and myenteric ganglia but not in ICC-DMP. Till now, from functional studies appears NKCC1 isn't involved in the generation of the pacemaker currents.

IMPLICATION OF VPAC1 RECEPTOR PHOSPHORYLATION IN AGONIST STIMULATED RECEPTOR INTERNALIZATION. C. Langlet, P. Vertongen, I. Langer, P. Robberecht. Lab Biochimie Erasme Bat G/E 808 route de Lennik 1070 Brussels.

Agonist-dependent phosphorylation is frequently associated with the internalization of G protein-coupled receptors through binding of arrestin that uncoupled the receptor from the effector and may be the first step of receptor internalisation. This sequence of events was not yet established for the VPAC1 receptor. Receptor phosphorylation was determined on membranes from cells prelabeled with ^{32}P -orthophosphate by immunoprecipitation with a specific monoclonal antibody followed by SDS-page and autoradiography. Internalization was measured by FACS technique using the same antibody labelling the external receptor domain. These parameters were compared in CHO cells expressing the wild type, truncated or mutated receptors in order to suppress the ser /thr intracellular residues. Carboxy-terminally truncated receptors identify three important sequences. Point mutations identified serine 435 and 455 and threonine 429. However, simultaneous substitution of these three amino-acids was not sufficient to completely abolish phosphorylation. We also focused on serine 250 residue, located in the second intracellular loop. Introduction of this last mutation in the truncated 1-421 completely abolished VIP stimulated phosphorylation. However, the combination of the 4 mutations maintained a residual signal, suggesting the implication of other residue(s) (which phosphorylation could be prevented in the truncated receptor due to the non-recruitment of kinase on the receptor). Internalization of the 1-429 and 1-421 receptors was markedly reduced. No single mutant presented an alteration of internalization even if their phosphorylation was diminished. The S435-455-T429A triple mutant was the only one to have an impaired internalisation. Furthermore, the shortest truncated receptor 1-398 that was not phosphorylated was normally internalised. The lack of correlation between the level of phosphorylation and of internalization must be interpreted cautiously : the full phosphorylation of the receptor is certainly not required for receptor internalization ; the possibility of internalization of a non phosphorylated receptor was observed only in severely truncated receptors and must be confirmed in a full size mutant.

DELINEATION OF THE MOTILIN DOMAIN INVOLVED IN DESENSITIZATION AND INTERNALIZATION BY USING FULL AND PARTIAL MOTILIN ANTAGONISTS. A. Mitselos, I. Depoortere, T. Peeters. University of Leuven.

The bio-activity of motilin is determined by the N-terminus, but studies with fragments indicate that the C-terminal region plays an important role in the desensitization of the motilin receptor (MTLR).

Aim : To verify this hypothesis we studied the desensitization induced by motilin analogs of different chain length with antagonist properties in contractility assays.

Methods : We used four motilin analogs of different chain length, abbreviated as cAnt-4, Ant-4, Ant-14 and Ant-22, corresponding respectively to a cyclical (GM-109) and a linear analogue (MA-2029) of motilin's N-terminal tetrapeptide developed by Chugai, and the [Phe³, Leu¹³]pMot(1-14) and [Phe³, Leu¹³]pMot(1-22) analogues discovered in our lab. Agonist induced Ca^{2+} luminescence was studied in CHO-K1 cells expressing the MTLR and the Ca^{2+} indicator apoaequorin (CHO-MTLR). Desensitization was studied by preincubation (2hrs) of cells with compound (10^{-5} M) prior to a second stimulation with motilin itself. Results were expressed as % of control (no preincubation). Internalization was visualized by stimulation of CHO-K1 cells, containing a MTLR C-terminally tagged with EFGP (Enhanced Green Fluorescent Protein, CHO-MTLR-GFP). Internalization was also quantified by determining the residual binding of ^{125}I motilin after 2hrs prestimulation with antagonists at 10^{-5} M.

Results : Ant-14 and Ant-22 had agonist activity although with low potency (pEC_{50} : 6.65 and 7.30 resp.), Ant-4 and cAnt-4 were essentially without agonist activity. Motilin and Ant-22 decreased the second response to motilin to resp. $18.6 \pm 4.5\%$ and $43.9 \pm 4.5\%$, whereas Ant-14, Ant-4 and cAnt-4 had no desensitizing effect (resp. $93.2 \pm 3.8\%$, $103.3 \pm 4.9\%$ and $92.2 \pm 3.9\%$). Residual ^{125}I -motilin binding was reduced more by the antagonists (99.6% Ant-4, 85% Ant-14, 97.5 % Ant-22) than by motilin (72%), with the exception of cAnt-4 (5%). Visualization of receptor trafficking in CHO-MTLR-GFP cells revealed that in contrast to motilin (decrease in membrane fluorescence : $18.7 \pm 3.2\%$) none of the antagonists induced receptor internalization.

Conclusion : The C-terminus of motilin enhances desensitization and internalization of the motilin receptor. Compounds with antagonist properties, due to modifications of the N-terminus, may change the conformation of the receptor and its affinity, without causing internalization. Our data suggest that potent agonists/antagonists may be developed without desensitizing properties.

ROLE OF THREE CONSERVED ACIDIC RESIDUES IN TM2 AND TM3 OF THE GHRELIN RECEPTOR. M. Van Craenenbroeck, I. Langer, P. Robberecht. Lab. Biochem. Erasme Fac. Med. ,1070 Brussels, Belgium.

Introduction : We previously established the importance of the positively charged amino-terminus of ghrelin on peptide affinity and peptide activity ; suppression of this charge (acetyl-ghrelin) reduced 20-fold the potency of the ligand on the receptor. According to these results, we searched a possible counter-ion in the receptor and pointed three acidic residues : D89 and D99 in TM2, and E124 in TM3 which are also present in the Motilin receptor.

Methods : The work was conducted on CHO cells stably transfected with wt and mutant receptors. The activity of the peptides was evaluated through the measurement of the increase of intracellular calcium by bioluminescence.

Results : D99N and E124Q mutants had a reduced affinity (10 and 20-fold respectively) for ghrelin ; ghrelin affinity for the D89N mutant was unchanged. To the contrary, N-acetyl-ghrelin had a 10-fold higher affinity for the D89N, D99N and E124Q receptors than for the wt receptor. Furthermore, the potency of the GHRP-6 was 500-fold lower for the E124Q mutant only.

Conclusion : The positive charge of the amino-terminus of the ghrelin interacts with the E124 and D99, not with the D89, but probably not through ionic bonds. The positive charge of the amino-terminus of GHRP-6 interacts only with E124, probably through an ionic bond. The increase of the potency of the acetyl-ghrelin could be explained if we suppose that acetylation allows new interactions between the -CO-NH- of the acyl function of the ligand and the newly introduced amide functions of the receptor.

DIFFERENTIAL DESENSITIZATION OF THE HUMAN GHRELIN RECEPTOR. L. Thielemans(1), J. Aerssens (1), D. Van de Wiel (1), M. Cik (2), A. Meulemans (1), B. Coulie (1). (1) Gastrointestinal and Emerging Diseases dpt., Johnson & Johnson Pharmaceutical Research and Development, a division of Janssen Pharmaceutica N.V., B-2340 Beerse, Belgium ; (2) Assay Development and HTS dpt. Johnson & Johnson Pharmaceutical Research and Development, a division of Janssen Pharmaceutica N.V., B-2340 Beerse, Belgium

Background. G-protein coupled receptors (GPCRs) undergo desensitization as a consequence of their activation. Our aim was therefore to study the occurrence of desensitization for the ghrelin receptor (GHS-R) and to investigate the paradigm that desensitization is directly linked to receptor activation.

Methods. Agonist-induced Ca^{2+} fluxes in Hek293 cells, stably expressing the GHS-R, were measured after loading with the fluorescent Ca^{2+} indicator Fluo-4-AM. Desensitization was studied by preincubation of the cells with ghrelin prior to a second stimulation with ghrelin for different periods (3 min, 10 min, 20 min and 60 min). Next, different agonists were preincubated at different concentrations for 3 min. Results were expressed as % of control response (no prestimulation). The negative logarithm of the preincubation concentration reducing the maximum response to ghrelin to 50% of its control value was calculated (pDC_{50}). The natural ligand ghrelin (human) and its derivatives des-ghrelin, the ghrelin fragments [1-5] amide, [1-14] and [23-28] were tested, next to the GHS-R agonists capromorelin and the hexapeptide GHRP-6.

Results. Ghrelin, capromorelin and GHRP-6 activated the GHS-R with a pEC_{50} of 9.10 ± 0.12 , 9.34 ± 0.12 and 9.42 ± 0.11 resp. Fragments [1-14] and [1-5] had a similar activity (8.29 ± 0.07 and 8.03 ± 0.08 resp.), whereas des-ghrelin and C-terminal fragment [23-28] were not able to evoke a Ca^{2+} response. Desensitization occurred rapidly, as the second stimulus was already reduced maximally after preincubation for 3 min with ghrelin $10^{-6}M$ ($8.50 \pm 3.67\%$; pDC_{50} 8.25 ± 0.06) compared to the incubation times of 10 ($5.2 \pm 3.7\%$; 8.99 ± 0.17), 20 ($14.7 \pm 3.2\%$; 8.38 ± 0.26) and 60 min ($6.9 \pm 2.1\%$; 8.83 ± 0.28). At 3 min preincubation, capromorelin and GHRP-6 desensitized with a pDC_{50} of 8.43 ± 0.16 and 8.82 ± 0.16 . Relative to its pEC_{50} , fragment [1-14] had a comparable result with a pDC_{50} of 7.81 ± 0.24 . As expected, no desensitization occurred with the inactive des-ghrelin and fragment [23-28]. Unexpectedly, fragment [1-5] did not induce desensitization of the GHS-R although it is an agonist with similar potency as fragment [1-14].

Conclusion. The GHS-R is desensitized rapidly. Most ligands have a desensitizing ability that corresponds to their potency to elicit a Ca^{2+} response. Fragment [1-5] is not consistent with this paradigm, analogous with data of motilin and substance P, supporting the idea that the ligand structure for receptor activation might differ from the structure needed to induce desensitization.

GASTRIC EMPTYING AND FOOD INTAKE IN GHRELIN KNOCKOUT MICE. B. De Smet (1), I. Depoortere (1), B. Moreaux (2), J. Tack (1), D. Moechars (2), B. Coulie (2), JP. Bosmans (2), TL. Peeters (1). (1) University of Leuven ; (2) Johnson and Johnson.

Ghrelin, is the first peripherally active peptide involved in the regulation of energy homeostasis with important effects on gastric emptying. To evaluate the physiological role of ghrelin, we compared food intake and gastric emptying in wildtype (WT) and ghrelin knockout (KO) mice and determined the effect of exogenous administration of ghrelin.

Methods : Ghrelin KO mice and the corresponding WT strain (129+C57BI) were developed in collaboration with Lexicon Genetics Inc. Cumulative food intake was followed after an overnight fast in 6 WT and 6 KO mice (n=3). The ¹⁴C octanoic breath test was adapted for mice, to measure gastric emptying in a sensitive and non-invasive manner. 6 WT or 6 KO fasted mice received a meal of chow and baked egg yolk, doped with 0.5 m Ci ¹⁴C octanoic acid. Excreted ¹⁴CO₂ was captured during 4h, counted and half emptying time (t_{half}) and lag period (t_{lag}) were calculated. Results are the mean of three consecutive breath tests in 6 mice with a time interval of 3 days. Ghrelin (75.4 nmol/kg) was administered ip 30 min before the meal.

Results : Initial body weight was similar between the WT and KO mice but after an overnight fast the KO mice lost more weight (10.52± 0.29% ; p<0.001) than the WT mice (8.53± 0.25%). Cumulative food intake after fasting did not differ between the WT (0.88±0.07 g) and KO mice (0.82±0.04 g) during the first 2h, but after that time point WT mice ate more and this became significant after 5h (p<0.05) and 6h (p<0.001). Body weight gain was consequently significantly higher in WT mice (1.23±0.14%) than in KO mice (0.74± 0.15%). The half emptying time of the solid meal in ghrelin KO mice (94.1± 3.8 min) was not significantly different (p=0.60) from t_{half} in WT mice (90.7± 4.4 min). The t_{lag} was also not affected. The maximal effective dose of ghrelin accelerated t_{half} in WT mice from 67.1± 6.3 min to 48.3± 5.9 min but not in the KO mice. However, similar to WT mice, t_{lag} was decreased significantly in KO mice from 40.2±3.0 min to 23.9±0.7 min.

Conclusion : The decreased food intake of KO mice is in agreement with ghrelin's orexigenic properties. Gastric emptying is normal in KO mice and is not affected by exogenous ghrelin. Absence of ghrelin, a change in receptor sensitivity or a downregulated receptor could trigger a compensatory mechanism to normalize gastric emptying.

STUDY OF SOMATOSTATIN LEVELS DURING THE EVOLUTION OF A SCHISTOSOMIASIS INFECTION IN LOW AND HIGH PATHOLOGY MICE. K. Van de Vijver (1), K. Kuypers (1), I. Depoortere (2), T. Peeters (2), J. Weyler (3), W. Jacobs (1), S. Chatterjee (1), E. Van Marck (1). (1) Labo Anatomopathologie, Universiteit Antwerpen ; (2) Labo Gastro-intestinale Hormonen,O&N, K.U.Leuven-Gasthuisberg, Leuven ; (3) Epidemiologie en Sociale Geneeskunde, Universiteit Antwerpen, Wilrijk.

Background & Aims : Schistosomiasis is a helminthic disease causing considerable morbidity and mortality worldwide due to fibrotic liver complications. The neuropeptide somatostatin exerts an antifibrotic effect on the hepatic stellate cells in vitro, and reduces fibrosis and morbidity in *Schistosoma mansoni*-infected animals. It is the drug of choice to control variceal bleeding and reduce portal pressure. The aim of the present study was to investigate the role of somatostatin in the evolution of *S. mansoni*-caused disease severity in two inbred mice strains, C57BL/6J (low pathology) and C3H/HeN (high pathology).

Methods : 40 C57BL/6J and 40 C3H/HeN mice were infected with 30 cercariae and sacrificed after 8 weeks (acute stage of infection) or after 16 weeks (chronic stage of infection) post-infection (p.i.). For each group 5 controls were included. Plasma samples were taken by cardiac puncture and the somatostatin levels were determined. The degree of liver pathology was examined quantitatively by egg count, measurement of granuloma volume and determination of hepatic hydroxyproline as a value for hepatic fibrosis.

Results : The C3H/HeN-strain showed a more severe pathology with significantly larger granulomas, more hepatic fibrosis and a higher mortality than the C57BL/6J-strain. Within each strain the mice had significantly more hepatic fibrosis in the chronic stage of the infection as compared to the acute stage. Somatostatin levels in the plasma of the C57BL/6J-strain rose significantly at 16 weeks p.i. (controls 146.00 ± 12.96 ng/ml vs infected 275.62 ± 23.48 ng/ml ; p=0,004), whereas no difference could be noticed at 8 weeks p.i. (controls 160,80 ± 17,24 ng/ml vs infected 191.53 ± 12.56 ng/ml ; p=0.238). In the C3H/HeN-strain higher somatostatin concentrations were found at 8 weeks p.i. (controls 160.40 ± 15.12 ng/ml vs infected 204.94 ± 7.85 ng/ml ; p=0.023) but not at 16 weeks p.i. (controls 191.20 ± 15.43 ng/ml vs 260.30 ± 29.49 ng/ml ; p=0.142).

Discussion : Somatostatin levels in the plasma may play a regulatory role determining the progression to severe or low pathology during *S. mansoni* infection. During the evolution of the infection somatostatin increases in the 'low pathology' C57BL/6J-mouse. C3H/HeN-mice only show an increase in somatostatin at 8 weeks, whereas in the chronic stage, when liver pathology worsens and mortality increases, the levels of this neuropeptide are not elevated.

PREVALENCE OF GASTRIC COMPLAINTS AND *HELICOBACTER PYLORI* INFECTION AMONG FLEMISH SEWAGE WORKERS AT MUNICIPAL WASTEWATER TREATMENT PLANTS. W. Van Hooste (1), A. De Schryver (2), M. van Sprundel (3). (1) IDEWE Occupational Health Services, Leuven ; (2) IDEWE & Dpt. of Public Health, University of Ghent ; (3) Dpt. of Epidemiology and Social Medicine, University of Antwerp, Belgium.

Objectives : In a health and hygiene questionnaire among sewage workers at Flemish municipal wastewater treatment plants (WWTPs) gastric complaints, peptic ulcers and gastroscopies were more often registered than among non-sewage exposed employees working for the same employer. The purpose of this pilot study was to evaluate 3 diagnostic *Helicobacter pylori* (*H. pylori*) tests in an occupational setting, to determine the *H. pylori* infection prevalence among WWTP workers and to test a possible association between work, gastric complaints and *H. pylori* infection.

Methods : The prevalence of *H. pylori* infection was determined by 3 noninvasive diagnostic tests in a cross-sectional study design. Mean age and exposure to wastewater/sludge were 37.1 years and 9.1 years respectively. Control groups were selected among participants in 2 Flemish studies.

Results : Three months' prevalence of gastric complaints was 40.2%. Overall prevalences of positive IgG and IgA antibodies were 21.9% and 13.0% respectively. Faecal antigen test was positive for 15.2% ; borderline positive for 3.3% of samples. 23.3% of the urea breath tests were positive. The IgG overall Prevalence Odds Ratio (POR), comparison with non-exposed group of Flemish administrative workers, 0.76 (0.44-0.98) (21.9% versus 29.1%). Comparison of employees 35 years and older with second control group, gave overall IgG POR of 0.93 (0.79-1.07) (30.1% versus 32.3%). No association was found between gastric complaints or compliance to industrial and personal hygiene measures and positivity in any of the 3 tests.

Conclusions : The occupational exposure at Flemish WWTPs do not cause an increased risk of *H. pylori* infection for sewage workers.

IDENTIFICATION OF '*HELICOBACTER HEILMANNII*' IN HUMAN GASTRIC BIOPSIES. K. Van den Bulck (1), M. Baele (1), D. De Groote (2), M. Stolte (3), R. Ducatelle (1), A. Decostere (1), F. Haesebrouck (1). (1) Department of Pathology, Bacteriology and Poultry Diseases, Faculty of Veterinary Medicine, Merelbeke, Belgium ; (2) Ghent University, Ghent, Belgium ; (3) Institut für Pathologie, Klinikum Bayreuth, Bayreuth, Germany.

Background & objectives : '*Helicobacter heilmannii*', a gastric human pathogen occurring in 0.2 to 0.6 % of the human stomachs, is probably originating from animals. The unculturability of this helical organism hampered the identification up to the species level. Morphologically and genetically, two types of '*H. heilmannii*' can be distinguished. '*H. heilmannii*' type I is highly related to '*Candidatus H. suis*', a porcine unculturable helicobacter species, while type II is highly related to the canine helicobacter species *H. felis*, *H. salomonis* and *H. bizzozeronii*, which are hard to distinguish from each other. The aim of this study was to identify non-pylori helicobacter species in human stomachs.

Materials & Methods : We recently developed a multiplex PCR for identification of *H. felis*, *H. salomonis*, *H. bizzozeronii* and '*Candidatus H. suis*' in gastric biopsies. Twenty-five human gastric samples, suspected to be '*H. heilmannii*' infected, were subjected to this PCR.

Results : *H. salomonis* was detected in 12 (48%) specimens tested, *H. felis* and *H. bizzozeronii* were each detected in 1 (4%) sample, while 2 (8%) samples tested positive for '*Candidatus H. suis*'. Six (24%) biopsy specimens tested negative in the PCR. Three samples (12%) were positive for both *H. salomonis* and *H. bizzozeronii*.

Conclusion : In the present study, *H. salomonis* was detected in 46% of the samples. This is in contrast with the study of Trebesius et al. (2001) who found 78% '*H. heilmannii*' type I and only 2.4% '*H. heilmannii*' type II in human biopsies. More samples will have to be tested to confirm that *H. salomonis* indeed represents the major part of '*H. heilmannii*' type II in human gastric biopsies.

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MULTIPLEX PCR-ASSAY FOR THE DIFFERENTIATION OF *HELICOBACTER FELIS*, *H. BIZZOZERONII* AND *H. SALOMONIS*. M. Baele (1), K. Van den Bulck (1), A. Decostere (1), P. Vandamme (2), M.L. Hänninen (3), R. Ducatelle (1), F. Haesebrouck (1). (1) Department of Pathology, Bacteriology and Poultry Diseases, Faculty of Veterinary Medicine, Merelbeke, Belgium ; (2) Department of Biochemistry, physiology and microbiology, Ghent University, Ghent, Belgium ; (3) Department of Food and Environmental Hygiene, University of Helsinki, Helsinki, Finland.

Helicobacter felis, *H. bizzozeronii*, and *H. salomonis* are frequently found in the gastric mucous membrane of dogs and cats. These large spiral organisms are phylogenetically highly related to each other. Their fastidious nature makes it difficult to cultivate them *in vitro*, hampering traditional identification methods. To enable discrimination of the three species, a multiplex PCR test was developed, based on the tRNA intergenic spacers and the urease gene. The length of the obtained amplicons was determined using capillary electrophoresis. This multiplex PCR assay was tested on gastric biopsies from 17 dogs, of which 13 were positive for *H. bizzozeronii*, one was positive for *H. felis*, and two dogs had a mixed infection of both species. In combination with previously described 16S rDNA-based primers specific for the non-culturable '*Candidatus Helicobacter suis*', our procedure may prove to be very useful in determining the species identity of '*Helicobacter heilmannii*'-like organisms observed in human stomachs and will facilitate research concerning their possible zoonotic importance.

GASTRIC *HELICOBACTER* SPECIES IN RABBITS : A HUMAN HEALTH HAZARD ? K. Van den Bulck, M. Baele, R. Ducatelle, F. Haesebrouck, A. Decostere. Department of Pathology, Bacteriology and Poultry Diseases, Faculty of Veterinary Medicine, Ghent University, Merelbeke, Belgium.

Gastric non-pylori helicobacters have been found in humans and a variety of pet animals, such as cats and dogs. Hitherto, no helicobacters have been reported to occur in rabbits, which are gaining in importance as companion animals. Stomach biopsies from 7/20 rabbits tested positive in a PCR assay amplifying a 400 bp fragment of the 16S rRNA gene using *Helicobacter*-specific primers. The entire 16S rRNA gene of the helicobacters present in these samples was amplified using consensus primers, cloned into a vector and sequenced. The 16S rRNA genes from four samples were highly similar to those of *Helicobacter heilmannii*, *H. felis*, *H. bizzozeronii* and *H. salomonis*. A multiplex PCR with primers against tRNA spacer regions and the urease genes revealed that one of the samples was positive for *H. salomonis*, while the other three samples were positive for *H. felis*. The 16S rDNA sequenced from the fifth sample showed 96% similarity to that of *H. pullorum*. The helicobacters hosted by the remaining rabbits could not be identified up to the species level. This study is the first to report the occurrence of *Helicobacter* species in rabbits. *H. felis* and *H. salomonis* are naturally colonizing the gastric mucous membrane of cats and dogs and are highly related to '*H. heilmannii*' in humans which is associated with human gastric disease. The presence of these species in the stomach of rabbits may indicate that not only cats and dogs but also rabbits might be a source of gastric non-pylori *Helicobacter* infections in humans.

DOES *HELICOBACTER PYLORI* INFLUENCE LIVER HISTOLOGY IN PATIENTS WITH CHRONIC HEPATITIS C ? S. Bakari (1), P. Langlet (1), L. Lasser (1), E.M Talib (1), C. Deprez (2), E. De Koster (1). (1) Dept Gastroenterology CHU Brugmann ; (2) Dept Pathology CHU Brugmann.

Aim : It was shown in the past that HCV-infected patients with liver cirrhosis (J Hepatol. 2000 ;33 :648-50) and with chronic HCV-related hepatitis (New Microbiol. 2003 ;26 :321-8) have a higher HP seroprevalence than age-matched blood donors. We wondered whether in HCV-infected patients present HP gastric infection might modulate liver histology and liver function tests.

Patients and methods : We detected the current presence of HP using Urea Breath Test in 38 consecutive HCV infected patients (26 male, 12 female, age 49.7 y +/- 14 [22-76]) who underwent liver biopsy for evaluation of the indication of antiviral treatment. 7 patients used >60 g alcohol/d. Activity and fibrosis were evaluated using the Metavir-score (0-4).

Results : All patients had chronic HCV hepatitis ; 7 had HCV-related cirrhosis. HP was present in 20 pts (13 M, 7 F) and absent in 18 (13 M, 5 F). None of the following were different in HP positive vs negative patients : age, gender, alcohol use, smoking, drug abuse, ASAT, ALAT, bilirubin, gamma-GT, alkaline phosphatase, WBC, hemoglobin, platelets. HP positive patients had a significantly higher fibrosis score (2.52 vs 2.05, Kruskal-Wallis p=0.04), and more often had cirrhosis (HP pos 6/18, HP neg 1/20, Fisher's exact p = 0.04).

Conclusions : In this small series, the current presence of HP was associated with an increased risk of liver fibrosis and cirrhosis in HCV infected patients. Although this does not prove causality, it raises the question whether HP is a risk factor for progression of HCV-related liver disease through fibrosis to cirrhosis (which should be investigated using a multivariate analysis in a large patient sample), and whether HP eradication might influence the outcome of HCV-related liver disease.

ANTIMICROBIAL RESISTANCE RATES OF *HELICOBACTER PYLORI* IN BELGIUM : PRESENTATION OF THE RESULTS OF THE 2003 NATIONAL SURVEILLANCE PROGRAMME. Y. Glupczynski (1), A. Burette (2), C. Berhin (1), G. Deboever, J-CI. Debongnie, M. Delforge, P. Deprez, V. Lamy, P. Lammens, Martinet JP, J. Reichling, P. Pescatore, Ph. Turk, and the Belgian *H.pylori* Study Group. (1) Microbiology Dept, Cliniques Universitaires UCL Mont-Godinne, (2) Gastroenterology Unit, CHIREC-Nouvelle Clinique de la Basilique, Brussels, Belgium.

Aim of the Study : The main determinants of success of treatment of *H. pylori* (*Hp*) infection are patient compliance and infection with antibiotic-resistant strains. Awareness of the local and national resistance rates of *H.pylori* for metronidazole, clarithromycin and fluoroquinolones is essential for effective treatment and to select the first line eradication regimen accordingly. There was thus an urgent need for annual national survey of antimicrobial resistance rates in Belgium because of the increasing incidence of *Hp* strains resistant to antibacterial drugs.

Method : 9 centres (able to performed the sampling and to freeze and keep the samples at -70°C for later collecting) agreed to participate to a national surveillance study of anti-microbial resistance of *Hp* strains to macrolides, imidazoles, amoxicillin, tetracycline, etc. The geographic distribution of the centres cover area located in the centre-north and centre-south of Belgium (Oostende, Hasselt, Brussels, Charleroi, Namur, Liège). The protocol was conducted during pre-defined 8 weeks period each year (may-june 2003) with collection of samples from ≥15-25 consecutive untreated patients who never received anti-*Hp* therapy (and had no history of recent antimicrobial, bismuth or PPI therapy within the last 2-3 weeks). Collection of the samples was organized 3 months after the end of the sampling period for central proceeding of the cultures (with the collaboration of Astra-Zeneca).

Results : The results of this study inquiry and of the yearly prevalence of resistance of *Hp* to antimicrobials will be presented at the Belgian Week meeting. Also, the last 2003 data concerning antimicrobial resistance rates from 5 different centres in Belgium who perform regularly *Hp*-cultures and antimicrobial susceptibility testing (Brussels 3x, Mont-Godinne and Charleroi/Jumet) will be presented. Overall, primary resistance rates averaged 30-35% to metronidazole and about 15% and for clarithromycin. Interestingly, about 20-25% of the isolates displayed high-level resistance to ciprofloxacin. This latter finding raises some concerns concerning the use of fluoroquinolones (e.g. levofloxacin) in rescue therapies in Belgium as it has been recommended by several teams in different European countries. Resistance rates were less than 2% for amoxicillin and tetracycline. Future surveys are warranted in order to monitor antimicrobial resistance trends of *H. pylori* strains in Belgium.

IS THE HISTOGENESIS OF CARDIAC CANCER SIMILAR TO GASTRIC CANCER, IN WHICH HELICOBACTER PYLORI-RELATED GASTRITIS IS THE PRECURSOR? A. Driessen, Dept. of Pathology, University Hospital Maastricht, Maastricht, The Netherlands.

Epidemiological studies reveal a decrease in incidence rates of the gastric adenocarcinomas, whereas the incidence of cardiac cancer have dramatically increased in developed countries. In parallel with cardiac cancer, the incidence of oesophageal adenocarcinomas is rising at an alarming rate. Some studies have shown that cardiac cancer and oesophageal cancer have some similar clinical features. Compared to gastric cancer, cardiac cancer has an even worse prognosis, which is related to the advanced stage of disease at the time of presentation. The different evolution in incidence rate as well the differences in clinical features suggests that gastric and cardiac cancer are two distinct entities. Whereas there is a clear relationship between Barrett's esophagus and esophageal adenocarcinoma, as well as between *Helicobacter pylori* and gastric cancer, the histogenesis of cardiac cancer is less obvious. Similar to gastric cancer, the development of cardiac cancer occurs according to a multistage model, in which an inflammation of the cardia may be the precursor. However the etiopathogenesis of this inflammation is less obvious. Our study, performed on patients with oesophageal, cardiac or gastric cancer, shows that chronic gastritis is more common in gastric (88 %) than in cardiac (56 %) and oesophageal adenocarcinomas (38 %). *Helicobacter pylori* is significantly more prevalent in gastric (73 %) than in cardiac (34 %) or oesophageal (21 %) cancer. Our results show that factors other than *Helicobacter pylori* must be involved in the histogenesis of cardiac cancer. Our study show that cardiac cancer shares some features of oesophageal adenocarcinomas and support the literature data of a similar etiopathogenesis.

WHAT'S NEW IN *H. PYLORI* THERAPY. P. Lammens. UCL – St. Jean, 1000 Brussels.

Following the European Maastricht Consensus, *first line Triple Therapy* (PPI – Clarithromycin and Amoxicillin or Metronidazole) with a success rate approaching 85 to 90% and *second line Quadruple Therapy* (PPI, Bismuth or Ranitidine-bismuth, Tetracycline 2 g and Metronidazole) are well defined.

We will discuss five trends. The two first ones are of immediate practical use. The last three ones are speculative or hope for the future :

1. Utility of *probiotics* to ameliorate both compliance and results.
2. Third (or second?) line therapy with *Levofloxacin* 500 mg, Amoxicilline and IPP.
3. Place of *Furazolidone* for low cost therapy and *Rifabutin* as rescue therapy.
4. What progress to wait with the *vaccine* into the new millenium. How to move from mouse to men?
5. Hope for *new target therapies*. The most promising is probably drugs targeting *UreI* (Urea Channel essential for *Helicobacter Pylori* survival).

INVITED LECTURE

EPIDEMIOLOGY OF H.PYLORI INFECTION AND INTRAFAMILIAL TRANSMISSION. J. Raymond. Paris, Saint Vincent de Paul.

Helicobacter pylori is a worldwide pathogen. In France its prevalence in a group of pregnant women was 21.5%, however it depends on the geographic origin of the women (11% in French women vs 50.6% in non French women). We observed a significant decrease of prevalence for French women since 1995. In children the prevalence was 15.8%. In children, the primary resistance to clarithromycin and to metronidazole was 21% and 43% respectively. This resistance depended also on the geographic origin of the children. We showed that the eradication rate of *H. pylori* after treatment depended mainly on the sensitivity of the bacteria against the used antibiotic (100% eradication in case of sensitivity to clarithromycin vs. 0% in case of resistance). The difficulty to eradicate the infection in one child, led us to search an intrafamilial contamination in both parents and in three siblings of the same family. To determine the relationships between isolates, two housekeeping genes (*hspA* and *glmM*) were sequenced for the strains of the family and compared with those of unrelated strains isolated from patients living in different geographic regions. All family members showed natural mixed colonization. The strains isolated from the children harbored identical or very similar alleles to those isolated from the parents, demonstrating that strains have circulated both between parents and children and between siblings. We observed several mechanisms enhancing strain diversity within this family (genetic drift, intragenic recombination and horizontal gene transfer). This study proved the presence of intra-familial dissemination of *H. pylori* strains.

LIVER TRANSPLANTATION USING LIVERS FROM SEPTUAGENARIAN AND OCTOGENARIAN DONORS : AN UNDERUSED STRATEGY TO REDUCE MORTALITY ON THE WAITING LIST. J. Pirenne, F. Van Gelder, D. Van Hees, D. Monbaliu, R. Aerts, W. Coosemans, C. Verslype, W. Vansteenebergen, P. Yap, J. Fevery, F. Nevens. UZ Gasthuisberg, Leuven, Belgium.

Mortality on liver transplantation (LTx) waiting list is increasing dramatically, approaching 20-30% worldwide. The use of older donors (>60y) has become an accepted practice to try enlarging the donor pool. The use of very old donors (>70y), however, remains scarce, due to possible underreporting of these donors and/or reluctance to use them given the risk of poor outcome. We report the outcome of LTx using septuagenarian & octogenarian donors and explore the possible reasons for the underuse of this large potential donor pool. Between 05/2001 and 10/2003, 6 livers were procured from very old donors (70,75,78,79,81,82) ; mean=77.5y and found transplantable ; 5 were female and 1 male. Cause of death was intracranial bleeding (ICB) (5) and trauma (1). Of note, 5 of these 6 donors originated from the same center that follows the policy of routinely contacting the Tx center for all brain-death patients before making final assessment as to their suitability for donation (Spanish-like-system). 5 patients {HCC (4), cryptogenic cirrhosis (1) ; 3 females, 2 males ; mean age 62.8 (54-69)} were successfully Tx. In a 6th patient, LTx was aborted due to the peri-operative discovery of extra-hepatic malignancy (HCC). Mean cold & warm ischemia times were 8.5hrs (5h49-13h35) & 55.2' (40'-78'), respectively. Graft function was immediate in all cases and peak transaminase was low : 682U/L (105-1489). Mean hospital stay was 21.8 days (14-29). Of the 5 LTx, 1 patient with a functioning graft died 2 months postTx (ICB). The other 4 are well. Patient and graft survival is 80%.

Conclusion : ICB&brain-death is an important cause of mortality > 70y but this age category currently represents a very small percentage of the donors used for LTx (4%) probably due to a) *underreporting* by donor teams who erroneously believe that these very old patients are not suitable donors, and b) *underuse* by recipient teams who fear that these livers may not work. Extremely advanced age is not *per se* a contra-indication to liver donation and successful LTx. Information to donor teams and establishment of a Spanish-like system (routine referral of all brain-death patients to Tx centers) is pivotal to allow maximal use of this large donor pool that could substantially reduce the mortality on LTx waiting lists.

LIVER TRANSPLANTATION USING CAVO-PORTAL TRANSPOSITION : AN EFFECTIVE TREATMENT IN PATIENTS WITH COMPLETE SPLANCHNIC VENOUS THROMBOSIS. J. Pirenne, B. Ceulemans, R. Aerts, D. Monbaliu, W. Coosemans, C. Verslype, W. Vansteenebergen, P. Yap, J. Fevery, F. Nevens. UZ Gasthuisberg, Leuven, Belgium.

A decade ago, segmental portal vein thrombosis was a contraindication to liver transplantation (LTx), but development of techniques such as thrombectomy and vascular interposition graft makes it nowadays possible to offer LTx to these patients. Complete and extensive thrombosis of the venous splanchnic system, however, is not manageable by conventional LTx techniques and is associated with a very poor short-term prognosis. Multivisceral Tx including the intestine has been done for this indication but remains a high-risk procedure. One alternative is the performance of a Cavo-Portal-Transposition (CPT) e.g. perfusion of the liver by recipient caval flow, but data on this procedure are very scarce. Therefore, results of LTx using CPT at a single-center were analyzed. Of 116 LTx done in a 2-year-period (05/2001-05/2003), 5 (4.3%) {2females/3males ; mean age : 53 (41-71) ; 3 Budd-chiari, 1 reTx/chronic rejection, 1 cryptogenic cirrhosis} undergone CPT. All had complete chronic splanchnic thrombosis (intraoperatively-confirmed) associated with advanced liver failure (child C), major portal hypertension and moribund condition. 2 had (sub)acute liver failure. CPT was done by completely diverting the inferior recipient vena caval flow into the graft vena porta directly (n=2) or via an interposition iliac vein (n=3). Normal anatomical infrahepatic caval flow was completely interrupted (n=5). Graft function was adequate in all 5 cases immediately postTx. Portal hypertension (ascites/varices/hypersplenism) substantially improved postTx but this was a slow process associated to a long hospital stay : 77days (17-145). Graft and patient survival are 100% at 3 mths ; 1 patient (71yo) died >3 mths due to biliary leak/sepsis unrelated to CPT. At last follow-up (8mth-2yr) liver synthesis capacity and gut function are satisfactory in the 4 survivors.

Conclusions : CPT represents a salvage procedure which provides adequate survival (80%) in moribund patients with diffuse splanchnic thrombosis not amenable to conventional LTx, and who would otherwise rapidly succumb. CPT avoids technically/immunologically more challenging multivisceral Tx. The intriguing observation that liver and gut can function satisfactorily in absence of direct anatomical portal drainage from the gut into the liver probably reflects the spontaneous development of extra-anatomical portocaval collaterals. One penalty of CPT, however, is the persistence of some degree of portal hypertension.

HCV GENOTYPE 4 IN BELGIUM : EPIDEMIOLOGICAL CHARACTERISTICS. C. Reenaers (1), J. Delwaide (1), C. Gerard (1), B. Bastens (2), B. Servais (3), A. Bekhti (4), E. Wain (5), G. Daenen (1), M. Delforge (2), T. Mesureur (1), B. Sente (6), + GLEVHE (7), J. Belaiche (1), A. De Roover (8), O. Detry (8), P. Honoré (8), M. Meurisse (8), B. Rentier (9), D. Vaira (9). (1)CHU Sart Tilman ; (2) St.Joseph Liège ; (3) Bois Abbaye Liège ; (4) Liège ; (5) La Tourelle Verviers ; (6) Waremme ; (7) Groupe Liégeois Etude Virus Hépatotropes ; (8) CHU Sart Tilman Chirurgie ; (9) CHU Sart Tilman Virologie.

In Western countries, patients (pts) infected with HCV genotype 4 are uncommon (5%) and are thought to be mostly from African origin. The higher prevalence of genotype 4 observed in Liège (11%) is thought to be related to the African immigration.

Aim of the study : to determine the genotype 4 patients' characteristics in our area.

Method : The files of 42 HCV genotype 4 pts were reviewed.

Results : Mean age was 42 ± 13 , with 55% females. Nineteen pts (45%) were from European origin without history of travel in Africa. In African pts, main modes of transmission were transfusion (26%), and infection of undetermined origin (70%). No IV drug users were found. In the opposite, among Europeans, IV drug users were found in 42%, and contamination of undetermined origin in 42%, while no contaminations by transfusion were observed. Subtypes 4a (4pts), 4e (4pts), and 4f (1pt) were exclusively encountered in Africans, while the 2 pts with subtype 4c were Europeans. Subtypes 4c/4d (17pts) and 4h (11 pts) were found both in Africans and in Europeans (4c/4d : Europeans 65% ; 4h : Europeans 46%). Among Europeans pts for whom mode of transmission was undetermined, half was originating from Italy or Portugal. A treatment with interferon (IFN) and ribavirin was given in 15 pts. The rate of sustained viral response (SVR) was 13%.

Conclusions : In our area, nearly half of genotype 4 pts are Europeans. In European pts, IV drug use was an important mode of transmission, as well as transmission of undetermined (sporadic) origin, while no contaminations with transfusion were found. The sporadic contaminations in Europeans seem to have occurred mainly in pts originating from Italy and Portugal. Treatment with conventional IFN and ribavirin gave a low rate of SVR.

CADAVERIC OR LIVING RELATED LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA : IS EXTENSION OF THE MILAN CRITERIA DELETERIOUS FOR TUMOUR FREE SURVIVAL? H. Van Vlierberghe (1), R. Troisi (2), I. Colle (1), M. Praet (3), B. de Hemptinne (2). (1) Dpt of Gastroenterology and Hepatology, (2) Dpt of Hepatobiliary Surgery and Liver Transplantation, (3)Dpt of Pathology, Ghent University Hospital.

Introduction : In patients with hepatocellular carcinoma (HCC) receiving a liver transplant, outcome is better if the number of lesions is low (equal or less than 3) and the size of the tumour is small (less than 5 cm in patients with a single tumour, less than 3 cm in patients having more tumours) (Milan criteria). Recently however more data are questioning these strict criteria and suggesting expansion of these criteria without compromising outcome. Prospective randomised trials are difficult to perform in this setting. However since living related liver transplantation (LRLTx), after informed consent of donor and recipient, can be performed in patients outside the Milan criteria, we compared outcome of liver transplantation for HCC between LRLTx and cadaveric liver transplantation (CLTx).

Materials and methods : In a retrospective way, outcome was compared between HCC patients receiving a LRLTx and CLTx. The Milan criteria were, as is clinically done, measured prior to transplantation. In patients outside the Milan criteria a LRLTx was more often proposed since, in the absence of clear data, we preferred not to compromise the cadaveric organ pool. Log rank testing and Kaplan Meier survival curves were used to test statistical significance.

Results : Patients (n=32) transplanted for a HCC between 6/1999 and 6/2002 were included (14 CLTx/18 LRLTx). Patients receiving a LRLTx were younger than CLTx patients (54 year \pm 5 versus 59 year \pm 6, $p=0.02$). LRLTx patients were more often outside the Milan criteria than CLTx patients (8/18 versus 2/14, $p=0.15$). There was no difference in follow up time between LRLTx and CLTx (665 days \pm 530 versus 532 days \pm 327, $p=NS$). Survival and HCC free survival were not different between the LRLTx and CLTx group (70 %). HCC free survival was significant lower for patients outside the Milan criteria than those within the criteria ($p=0.01$, fig). However patients outside the Milan criteria without vascular invasion had a similar outcome as patients within the criteria.

Discussion : Outcome in HCC patients receiving a CLTx or LRLTx was not different. When patients with vascular invasion are excluded, extension of the Milan criteria does not impair outcome after liver transplantation. However before implementing more liberal rules for HCC patients on the waiting list, more data are definitely needed.

SCREENING FOR HEPATOCELLULAR CARCINOMA IN CIRRHOSIS : A RETROSPECTIVE SINGLE CENTRE EXPERIENCE. J. van Dongen, S. Franque, P. Pelckmans, P. Michielsens. Gastro-Enterology Hepatology, Antwerp University Hospital, Edegem, Belgium.

Introduction : Hepatocellular carcinoma (HCC) represents more than 5% of the newly diagnosed malignancies annually, and its incidence is increasing. It mostly originates in a cirrhotic liver, with hepatitis B, hepatitis C and alcohol abuse as the most common underlying causes. Although potentially curative treatments are available, prognosis is often poor, probably because diagnosis is established at an advanced state. Therefore screening guidelines in cirrhotic patients have recently been developed¹. It remains questionable, however, if screening improves outcome.

Aims & Methods : We retrospectively analysed the 48 cases of HCC diagnosed at our institution between January 1st 1992 and March 31st 2003. Patients were divided in 2 groups, according to diagnosis by screening of cirrhotics (by determination of alpha-fetoprotein and abdominal ultrasound q 3-6 months) or incidental diagnosis. The 2 groups were compared for tumour status, treatment and survival. Statistical analysis included Student t-test, Chi square, Kaplan-Meier plots and log rank test when appropriate.

Results : In 16 (33.3%) patients HCC was discovered by screening (screening group), in 32 (66.7%) diagnosis was made incidentally (incidental group). There were no significant differences between the 2 groups regarding age, gender, aetiology or severity of liver disease (Child-Pugh score). The overall 6 month survival rate was 50%, but was significantly better in the screening group (90.9% vs. 30.4% in the incidental group ; $p=0.001$). The 1 and 2 year survival rates were also better in the screening group (60.0% and 33.3% respectively, vs. 31.8% and 14.3% in the incidental group), but without reaching significance. Kaplan-Meier plot showed a significantly better survival curve for the screening group (log rank test : $p=0.017$). In this group more potentially curative treatments were performed (81.3% vs. 40.0% ; $p=0.027$), indicating a less advanced stage with a better prognosis. The tumours were smaller in the screening group compared to the incidental group (80.0% vs. 41.9% ; $p=0.015$). Other tumour characteristics such as the number of nodules, vascular invasion and metastases were not significantly different.

Conclusion : Although the analysis is retrospective and the number of patients rather small, we may conclude from our results that screening for HCC in patients with cirrhosis leads to an earlier diagnosis in a less advanced stage, allowing for more potentially curative treatments and leads to a better survival rate.

SEVERE COLITIS IN YOUNG MALE ADULTS TRANSPLANTED FOR PSC. O. Buchel (1), C. Verslype (1), G. Van Assche (3), F. Nevens (1), R. Aerts (5), A. Dhoore (6), J. Pirenne (5), J. Fevery (1). (1) Hepatology, (3) Gastroenterology, (5) Abdominal Transplantation Surgery, (6) Abdominal Surgery, KU Leuven/UZ Gasthuisberg, Leuven.

A high incidence of active inflammatory bowel disease (IBD) following liver transplantation (LT) for PSC was noted. We looked for predictive factors by analysing 22 consecutive PSC patients who underwent LT ; 12 had IBD before LT (one received colectomy at LT). De novo IBD was not seen in this group, but severe exacerbations occurred in 5 (45 %), mild colitis in 2 (18 %) of 11 at risk for exacerbation. IBD was refractory in 3, leading to death ($n=1$) or total colectomy ($n=2$). Those with severe IBD were young (25-39 yr) and males, in contrast to an equal gender ratio in the other 14. Time between LT and IBD-relapse varied from 0.5 to 26 months. Unexpected IBD-sparing of the rectum was found in 6/7. IBD-relapse occurred in 4 while still on steroids (4-16 mg methylprednisolone). Interestingly, 5 had antinuclear (ANA) and 3 had smooth muscle antibodies (SMA) $>1/80$ at presentation with PSC. HLA B8 and DR3 was more prevalent in the affected group. Neither the type of immunosuppression nor CMV-mismatching did play a role. Upsurge of active (most often mild) IBD was seen in only 20% ($n=8$) of 40 PSC+IBD patients not having LT, contrasting with 64 % in the LT group. In conclusion, young age, male gender, diagnosis of IBD prior to LT, immune-related disorders, positive ANA/SMA and HLA type B8 and DR3 are associated with exacerbations of severe colitis with sparing of the rectum. Upsurge of IBD was seen while still on steroids in 4 patients.

INVITED LECTURE

AUTOIMMUNE HEPATITIS/SCLEROSING CHOLANGITIS OVERLAP SYNDROME IN CHILDHOOD. G. Mieli-Vergani, A. Mowat. Paediatric Liver Service, Institute of Liver Studies, King's College Hospital, Denmark Hill, London, SE5 9RS, UK.

Sclerosing cholangitis (SC) in childhood is a heterogeneous condition with different aetiologies. In contrast to the experience in adults, sclerosing cholangitis occurring as an idiopathic disease (primary sclerosing cholangitis) is rare. The most common type of SC in childhood is autoimmune sclerosing cholangitis (ASC), an overlap syndrome between autoimmune hepatitis and SC. The clinical, biochemical, immunological and histological presentation of ASC is often indistinguishable from that of AIH. In both conditions, there is an increase in IgG, presence of circulating non-organ specific autoantibodies, and inflammatory histological features, including interface hepatitis. A prospective study over a period of 16 years¹ shows that children with ASC respond to immunosuppressive treatment with prednisolone and azathioprine satisfactorily and similarly to AIH in respect to remission and relapse rates, times to normalization of biochemical parameters, and decreased inflammatory activity on follow up liver biopsies. However, the cholangiopathy can progress on treatment, suggesting that prednisolone and azathioprine are effective in abating the parenchymal inflammatory damage, but may not be as effective in controlling the bile duct disease. Moreover, there may be evolution from AIH to ASC over the years, despite treatment. Whether the juvenile autoimmune form of sclerosing cholangitis and AIH are two distinct entities or different aspects of the same condition, remains to be elucidated.

1. Gregorio G et al. Autoimmune hepatitis/sclerosing cholangitis overlap syndrome in childhood : a 16-year prospective study. *Hepatology* 2001 ; 33 :544-553

ENDOSCOPIC THERAPY OF CHRONIC PANCREATITIS IN CHILDREN. M. Arvanitakis (1), M. Delhaye (1), M. Daguzan (1), C. Matos (2), M. Cremer (1), J. Devière (1). (1) Dpt of Gastroenterology, (2) Dpt of Radiology, Erasme University Hospital.

Background : Chronic pancreatitis (CP) occurs rarely in children and the most frequent presentation is recurrent attacks of pain. The aim of this study was to evaluate the effect of endoscopic ductal drainage on pain relief in children with CP.

Patients : During a period of 10 years (1991-2001), 20 children with CP had endoscopic therapy at the mean age of 9 years (2-15). Clinical status was evaluated after therapy, based on the number of hospital admissions during follow-up (FU).

Results : The most frequent presentation of CP was recurrent episodes of acute pancreatitis (AP) (n=16, 80%). Mean age of onset of symptoms was 6.5 years (1-15) and mean age of diagnosis was 7.5 years (3-15). Seven children (35%) had hereditary pancreatitis associated with cationic trypsinogen mutation. CP was characterized as severe according to the Cambridge classification in 15 (75%) children. Mean duration of disease (between onset of symptoms and endoscopic treatment) was 31 months (1-84). Two children had exocrine insufficiency (n=2, 10%), and one of these patients also had diabetes. Four patients (20%) had complete pancreas divisum. Pancreatic calcifications were observed in 14 (70%) patients. Endoscopic therapy consisted of pancreatic sphincterotomy of the major (n=18) and/or the minor (n=5) papilla for all patients. Extracorporeal shock wave lithotripsy for pancreatic calcifications followed by fragment stone extraction was required in 4 and initial pancreatic stenting in one patient. Mean FU of 72 months (3-144) was obtained in 17 children. Results were excellent in 11 patients (d 2 admissions during FU) and satisfactory in 4 patients (> 2 admissions during FU and further endoscopic therapy). Finally, poor results were observed in 2 children, who required surgery and/or frequent endoscopic therapy.

Conclusions : Therapeutic ERCP in a pediatric population of CP can lead to clinical improvement and can be considered as the initial treatment of choice.

ENDOSCOPIC TREATMENT FOR MAIN PANCREATIC DUCT RUPTURE FOLLOWING VERTICAL BANDED GASTROPLASTY. M. Arvanitakis (1), R. Chamlou (2), M. Delhaye (1), C. Matos (3), J. Closset (2), J. Devière (1). (1) Dpt of Gastroenterology ; (2) Dpt of Digestive Surgery ; (3) Dpt of Radiology, Erasme University Hospital.

Background : Acute pancreatitis (AP) has been described as a rare complication of Silastic ring vertical banded gastroplasty (SRVG). It can be attributed to a pancreatic trauma occurring during surgery leading to ductal injury, AP and formation of pancreatic fluid collections (PFC). Endoscopic therapy is technically difficult in these patients, because of the presence of the small outlet channel formed by the ring, which limits the access to the distal part of the stomach and the transmural endoscopic approach of adjacent PFC.

Patients and Methods : In this study, we report 4 cases of patients undergoing SRVG (4 women, median age : 33 years (19-50)) for morbid obesity who presented AP post-operatively, accompanied by main pancreatic duct disruption (MPDD) and PFC. All patients had endoscopic treatment for symptomatic PFC (pain for 2 patients and sepsis for 2 patients).

Results : During a period of 16 months, out of 150 SRVG performed in our institution, AP associated with MPDD was recorded in 2 patients. Another two patients with identical presentation were referred from other institutions for endoscopic treatment. AP occurred at a median of 4 days (4-6) after SRVG and MPDD (located at the body and tail junction) was documented 10 days (6-35) after SRVG by means of S-MRCP. Median interval between SRVG and endoscopic treatment was 15 days (7-45). All four patients had transmural drainage of PFC (median maximal diameter : 80mm (70-100)) by means of cystogastrostomy, under endoscopic guidance (n=4), associated with endoscopic ultrasonography (n=2) and/or fluoroscopic guidance (n=4), followed by the insertion of one or more double pig-tail 10F plastic stents. Two patients had complementary transpapillary drainage including pancreatic sphincterotomy (n=2) and plastic 10F stenting (n=1). Access to the distal gastric cavity through the outlet channel with the duodenoscope was technically difficult in all patients requiring the use of a guidewire, associated with pneumatic dilation up to 20 mm of the outlet channel in 2 patients. Endoscopic therapy was successful in all patients, with subsequent resolution of PFC. During a median follow up of 10 months (4-12), only one patient required further endoscopic drainage for a recurring PFC, 6 months following initial treatment.

Conclusions : AP with MPDD is a rare but serious complication of SRVG. Endoscopic therapy can be considered as a first-line therapeutic option, although it is technically elaborate.

SOMATOSTATIN ADDED TO A TPN-MIXTURES IN THE TREATMENT OF FISTULA. G. Roeyen (1), T. Chapelle (1), H. De Bosscher (2), E. Mattheeussen (2), M. Ruppert (3), D. Ysebaert (1). (1) University Hospital Antwerp, Depts. of Hepatobiliary, endocrine and transplantation surgery ; (2) University Hospital Antwerp, Nutrition team.

Study objective : Somatostatin and total parenteral nutrition (TPN) are routinely used in the treatment of pancreatic and enterocutaneous fistula. This study was performed to determine whether somatostatin should be administered by a separate intravenous line, or could be added safely to the TPN-mixture. When somatostatin is added to a TPN-mixture, only one intravenous line is needed for administration of both drugs, leading to less manipulation by the nursing staff and therefore less administration errors.

Methods : 8 patients with a pancreatic or a enterocutaneous fistula were treated with a standard TPN-mixture (Kabiven 14 - Fresenius) and somatostatin (Somatostatin-UCB ®) 6 milligram per day. When somatostatin was added to the TPN-mixture, samples drawn immediately after preparation, 4 and 24 hours after preparation were analysed to determine somatostatin availability. Patients were randomized to two possible treatment regimens : 'TPN with somatostatin added - TPN and somatostatin separately - TPN with somatostatin added' or 'TPN and somatostatin separately - TPN with somatostatin added - TPN and somatostatin separately'. Each regimen consists of 9 days of therapy and was continued in a separate setting when clinically necessary. During treatment, serum levels of somatostatin were measured daily and pre- and post-treatment samples were also analysed.

Results : Samples drawn from the mixture, immediately, 4 hours and 24 hours after preparation demonstrated a somatostatin availability of more than 100.000 picogram per milliliter. Normal values of endogenous somatostatin rank below 110 picogram per milliliter. When somatostatin was infused through a separate intravenous line, the mean patient's serum level of somatostatin was 932 picogram per milliliter (SD = 546). When somatostatin is added to the TPN and infused 'all in one', mean serum level of somatostatin was 905 picogram per milliliter (SD = 477). The mean pre- and post-treatment serum level was 19 picogram per milliliter (SD = 7).

Conclusion : When added to a TPN mixture somatostatin is still fully available in the TPN-mixture 24 hours after preparation. The mean serum level of somatostatin are comparable in both treatment regimens. Therefore somatostatin can be added safely to a TPN-mixture.

URGENT OR DELAYED LAPAROSCOPIC CHOLECYSTECTOMY FOR ACUTE CHOLECYSTITIS : A COMPARATIVE STUDY. T. Chapelle, B. Bracke, G. Roeyen, D.K Ysebaert. Dept. of Hepatobiliary, Transplantation and Endocrine surgery, University Hospital of Antwerp.

Objective : Laparoscopic cholecystectomy for acute cholecystectomy can be performed within five days after the onset of symptoms (urgent cholecystectomy) or after six weeks of antibiotic treatment (delayed cholecystectomy). We compared both methods on clinical outcome and economic impact.

Material and methods : We retrospectively looked at all laparoscopic cholecystectomies performed for cholecystolithiasis (n patients = 128) in our department in 2001-2002 ; we excluded combined surgical procedures. In a first group we analyzed the patients who underwent an urgent cholecystectomy for acute cholecystitis (n = 39) ; in a second group the patients who underwent a cholecystectomy after antibiotic treatment (n = 36) ; and in a third group the patients who had an elective cholecystectomy for symptomatic cholecystolithiasis (n = 53). The latter was considered as a control group. We reviewed the medical history, the therapeutic success of prolonged antibiotic treatment, the surgical conversion rate, the complication rate and the final outcome. We tried to make an economic analysis of both approaches : we compare the duration and costs of hospital stay and the cost of antibiotic treatment. We did not take into account the cost of preoperative diagnosis and of the surgery, because they were similar in all groups.

Results : Demographics and medical history was similar in groups 1 and 2. In group 2, antibiotic treatment was unsuccessful in 23/36 patients (65%) ; this means that in those patients surgery was performed earlier than six weeks after the onset of symptoms (mean 33 days after onset of symptoms). This was due to ongoing symptomatic cholecystitis. The surgical conversion rate was 0/39 in group 1 and 2/36 in group 2 (0% vs. 5,6%). Postoperative complication rate were similar in both groups. There was no postoperative mortality. Hospital stay and costs related hereto were much longer in group 2 than in group 1 and 3 (15,4 vs. 6,9 vs. 5,1days). Costs for antibiotics were higher in group 2 than in group 1 and 3 (373 vs. 200 vs. 31).

Conclusion : In 2/3 of the patients, antibiotic treatment is not successful in delaying surgery for 6 weeks. There is no extra postoperative morbidity and mortality in urgent cholecystectomy compared to delayed cholecystectomy. There is an important extra cost when delaying cholecystectomy. This is due to longer hospital stay and more antibiotics. Therefore, we recommend to perform urgent cholecystectomy in acute cholecystitis.

ADAPTATION OF THE EATING PATTERN IN ACHALASIA AND ITS IMPACT ON CONVENTIONAL SYMPTOM SCORING. S. Sengier, D. De Looze, G. Van Maele, M. De Vos. University Hospital Gent, Belgium.

Aim Achalasia patients often adapt their eating pattern in order to avoid dysphagia or regurgitation. This changed behaviour may underestimate the real status of a patient if the conventional scoring systems are used, asking about dysphagia, regurgitation and pain.

Methods An exhaustive questionnaire about eating pattern, adaptational behaviour, food avoidance, quality of life etc. is offered to patients with achalasia and compared with the Eckhardt score. The questionnaire is sent by mail and filled out by the patients at home. From this questionnaire a score can be derived. In the same period a modified Eckhardt score (dysphagia, regurgitation, retrosternal pain) is taken by the physician at time of consultation or by telephonic interview. Statistics : Spearman rank correlation coefficient.

Results One hundred and twenty patients received the questionnaire of which 75 responded and 53 forms were evaluable. There were 23 females and 30 males with a mean age of 52 y (7-83). Previous therapy consisted of pneumatic dilation (26), myotomy (15), botulinum toxin (11) and untreated (1). The mean Eckhardt score was 2,2 (0-7), with no difference between the treatment groups. None of the patients considered a therapeutic procedure necessary at the time of questioning. In 40 % of the patients however adaptation of the eating pattern was found by means of the questionnaire : position, drinking, quantity, soft foods, etc. A good correlation was found between the Eckhardt system and the questionnaire as for the total scores and the dysphagia score (rs=0,655 and rs=0,638 respectively, both P<0,001). Specific query of tolerance/avoidance of different foods showed more positive correlations with the questionnaire than with the Eckhardt score. With the questionnaire there was a positive correlation with adapted intake of fluids, meat, cereals, fruits, vegetables and milk derivatives. With the Eckhardt score this was only found with cereals, fruits and milk products. As for the quality of life, best correlation was found with the questionnaire.

Conclusion Despite the fact that treated achalasia patients feel well and ask no further treatment, 40 % of them adapt their feeding pattern. The Eckhardt score correlates well with a more exhaustive questionnaire, but this latter reveals more thoroughly a change in eating pattern, especially through adapted position and avoidance of given foods. Bad influence on the quality of life is also found to be more pronounced by means of a questionnaire.

THE LAPAROSCOPIC NISSEN FUNDOPLICATION AS TREATMENT OF GASTROESOPHAGEAL REFLUX IN CHILDREN : AN EVALUATION OF 106 CONSECUTIVE PROCEDURES. W. Coosemans, PH. Nafteux, J. Mathed, T. Tollens, G. Decker, P. De Leyn, D. Van Raemdonck, I. Hoffman, C. Deboeck, M. Proesmans, V. Janssens, T. Lerut. University Hospital Leuven.

Background : Nowadays the laparoscopic Nissen fundoplication has become a frequently performed procedure in children who suffer from gastroesophageal reflux disease (GERD), especially when medical treatment fails. In this study we describe our 8-year experience with 106 consecutive laparoscopic Nissen funduplications. The aim of this study was to assess the indications for surgery, the per-and postoperative complications and the patient's satisfaction degree. **Methods** : From January 1994 to May 2002, we included 106 consecutive patients (aged 8 months to 18 years). The indications were symptomatic GERD (resistant to medical treatment), pulmonary symptoms or combinations of both. The patient's satisfaction was assessed by questionnaire.

Results : No mortality was noted and conversion to an open procedure was necessary in 3 cases (2.8 %). Major post-operative complications were seen in 10 % of cases. Recurrence of reflux occurred in 6 patients (3 due to herniation of the fundoplication). Dysphagia was seen in 22% of cases with spontaneous regression in all but 6 patients (4 dilations, 2 redo Nissen). Gas bloating occurred in 11 % of the children, all with spontaneous regression. Recurrent pneumopathies were seen in 7.4% of the patients who presented with reflux-related pneumopathies. The greater part of these patients showed an improvement in pulmonary symptoms compared with the preoperative situation. 71 % of the children sent back their questionnaire. 30 patients (41.6 %) gave the maximum score and 92% of the patients presented a good quality of life and a decrease in preoperative symptoms.

Conclusion : This study shows that the laparoscopic Nissen fundoplication can be performed safely in children with low complications and good reflux control showing symptoms improvement and high satisfaction score in most of the patients. Good follow-up of the patients remains in any case mandatory.

POTENTIAL INCREASE OF EXPENSES FOR ANTI SECRETARY DRUGS IN BELGIUM : A FORECAST MODEL AND A PLEA FOR CONDITIONAL REIMBURSEMENT. M. Deltenre, P. Schutyser, B. Shockaert Astrazeneca Belgium.

Background : Estimated Inami/Riziv 2002 expenses for H2 antagonists (AH2) and PPI's reimbursement were around 146 million €. In 2003, projected expenses might increase up to 175 million €, probably because of growing prescriptions of generics and unconditional reimbursement of Rabeprazole.

Methods : To evaluate future expenses in that field, a model was developed taking on account the potential increase of GORD patients (from 150000 in 1998, 282000 in 2000, 445000 in 2003 and up to 900000! within 2.5 to 6 years), of NSAID users coverage (currently 380000 patient year) and dyspeptic patients (currently 115000 patients, potentially up to 588000). Three reimbursement situations have been simulated : 1. On-going current mixed Bf/B reimbursement conditions. 2. Bf/C regulation based on a 15% price reduction of brand PPI's. 3. 'All in B' situation with a 40% price

TABLE 1	Bf/B	C -15%	Bf -15%	B -40%
PPI	31,92	22,64	27,17	21,62
PPI gen	17,92	13,62	17,87	17,82
AH2	9,55	6,80	-	9,55

reduction for brand PPI's. A monthly weighted treatment cost for AH2, generic and brand PPI was calculated according to July 2003 market shares (Table 1, cost expressed in €).

Results : projected Inami/Riziv costs and amount of treated patients are summarized in Table 2.

Conclusion : Beside a much better respect of good clinical practice and guidelines, a system allowing short empiric treatment course (C reimbursement) and a diagnosis-based, long-term treatment (B reimbursement after endoscopy) would avoid a dramatic increase of expenses for anti secretary drugs reimbursement and would be balanced with claims for possible savings in UGI endoscopy load, currently estimated around 11 million €/year.

TABLE 2	TOTAL		RATIO	
	Cost M€	Pat (0000)	Cost	Patients
Current situation	175	86	1,0	1,0
Current bf/b prognosis	334	185	1,9	2,2
bf/c - 15 %	188	185	1,1	2,2
all in b -40%	277	185	1,6	2,2

REPEATED LIVER CELL TRANSPLANTATION VIA PORTH A CATH SYSTEM IN A CHILD CRIGLER NAJJAR SYNDROME. X. Stephenne (1), M. Vanderborcht (1), M. Najimi (2), , C. Calliau (1), F. Smets (1), R. Reding (1), de Ville (1), J. de Goyet (1), I. Jankowska (1), E. Swiatkowska (1), E. Sokal (1). (1) Liver cell transplantation program, UCL, Brussels. ; (2) Institute 'Pomnik-centrum Zdrowiak Dziecka', Warsawia, Poland.

Liver cell transplantation is a novel experimental approach for the treatment of inborn errors of liver metabolism. We report a repeated cell infusion approach via a Porth a Cath system for the treatment of an eight year's old girl with Crigler Najjar Syndrome. Hepatocytes were isolated from the left liver segment of one female and two male identical donors using the classical two step collagenase perfusion method. Cell recovery accounted for 3.8, 2.1 , and 2.15 billions respectively, and viability ranged between 81 & 87 % (Trypan Blue exclusion method). A Porth A Cath system was inserted into a jejunal vein, and the access chamber placed sub-cutaneously in the left hypochondrion. 1.9 billion fresh isolated hepatocytes were first infused over two hours. The child received then five separate infusions for a total of 4.18 billion hepatocytes. The fourth first infusions used fresh liver cells, whereas cryopreserved cells were infused for the subsequent 5 infusions. The procedure was well tolerated, without any change in portal blood flow and portal pressure following the infusions. She received triple immunosuppression including anti IL2r antibodies (Simulect, Novartis, Bâle, Sw), tacrolimus (Fujisawa, Berlin, G) and steroids. Transplantation efficiency was evaluated by measuring total Bilirubin levels, under identical phototherapy program. Mean bilirubin level during the five years before transplantation were 17.5 ± 0.49 mg/dL. The level dropped to 16.16 ± 0.31 mg/dL after the first infusions * $p < 0.05$ and to 15.08 ± 0.27 mg/dL after the second infusions. Six months after the first infusion, and the total of nine infusions, bilirubin levels had decreased progressively (13.6 ± 0.42 mg/dL *** $p < 0.001$) to reach the lowest value of 11.4 mg/dL. The effect of LCT was however not persistent, and bilirubin returned thereafter to pre- transplant values from month 6 post-LCT. The reason for the loss of metabolic effect could be rejection or apoptosis of transplanted cells.

Conclusion : Liver cell transplantation can be done safely and repeatedly via a permanent portal access system, using a Porth A Cath. Metabolic effect in this case was temporary, which means that repopulation did not occur despite original efficient engraftment.

HETEROGENEITY OF DYSPEPSIA IN THE GENERAL POPULATION IN BELGIUM. H. Piessevaux (1), B. De Winter (2), J. Tack (3), E. Louis (4), V. Muls (5), D. De Looze (6), P. Pelckmans (2), M. Deltenre (5), D. Urbain (7). Gastroenterology Depts (1) UCL St-Luc Brussels ; (2) UZ Antwerpen ; (3) KULeuven ; (4) CHU Liège ; (5) ULB Brussels ; (6) UZ Gent ; (7) AZ VUB Brussels.

Several surveys have addressed the prevalence of dyspeptic symptoms in the general population. Recent observations suggest considerable heterogeneity in patients with dyspepsia (Dysp) seen in tertiary care centers (Fischler 2003). The

Aim : The present study was to investigate the distribution of Dysp symptoms in the general Belgian population.

Methods : A face to face interview constructed on 26-items including the profile of dyspeptic symptoms was performed in a representative population sample. A four-item heartburn questionnaire was used to identify co-existing GERD (Johnson 1987). A univariate analysis was performed to determine the correlation between cofactors and the symptom

	A	B	C
Fullness	.821	.128	.183
Bloating	.820		.199
Early satiety	.693	.347	.144
Vomiting	.144	.905	
Nausea	.190	.892	
Discomfort	.263		.672
GERD score	.154		.663
Pain	.306	.109	.645
Belching	.148	.350	.606

pattern. A factor analysis of the symptoms was conducted.

Results : A cohort of 2025 subjects above 15 years of age was interviewed : 417 (20%) experienced stomach or digestion problems in the past 12 months : 222 (11 %) qualified as Dysp (Dysp+Refl-) alone, 148 (7%) had co-existing GERD (Dysp+Refl+), 43 (2%) had minimal symptoms (Dysp-Refl-) and 4 (0.2%) had reflux symptoms only (Dysp-Refl+). In univariate analysis, NSAID use was associated to the Dysp+Refl- symptom profile. Factor analysis revealed three factors : one associated with early satiety (A), fullness and bloating, a second associated with nausea and vomiting (B) and a third with discomfort, pain and belching (C).

Conclusions : Dysp symptoms are very common in the Belgian population. NSAID use is a risk factor but accounts at best for only a small subset of the patients. Statistical analysis identified three underlying factors, which partly correspond to the heterogeneity identified in tertiary care patients. Dyspepsia in the general population is a heterogeneous disorder and it is conceivable that the underlying pathophysiological factors are similar to those in tertiary care. (Sponsored by a grant of Astra Zeneca, Belgium)

CARD15 MUTATIONS IN PATIENTS WITH SPONDYLOARTHROPATHIES IDENTIFY A SPECIFIC PHENOTYPE RELATED TO CROHN'S DISEASE. H. Peeters (1), D. Laukens (2), D. Marichal (1), M. Van Den Berghe (3), D. Elewaut (3), F. De Keyser (3), H. Mielants (3), C. Cuvelier (4), E.M Veys (3), E. Remaut (2), L. Steidler (2), M. De Vos (1). (1) Ghent University Hospital, Dept. of Gastroenterology ; (2) Ghent University, Department of Molecular Biomedical Research-VIB ; (4) Ghent University Hospital, Dept. of Rheumatology ; (4) Dept. of Pathology.

Objectives : Association between spondyloarthropathy and Crohn's disease is a well-known phenomenon. We investigated whether the reported mutations in CARD15, a susceptibility gene for Crohn's disease, can be used as a marker for intestinal inflammation observed in spondyloarthropathy.

Methods : Fifty-nine patients with spondyloarthropathy without evidence for Crohn who underwent an ileocolonoscopy with histology between 1983 and 1989, were clinically re-evaluated. Using RFLP-PCR, we assessed the prevalence of three single nucleotide polymorphisms in CARD15 and compared them to ethnically matched Crohn and control populations.

Results : The carrier frequencies of R702W, G908R and 1007fs in spondyloarthropathy and control populations were 22% and 15% but increased to 42% in the subgroup of spondyloarthropathy patients with chronic gut inflammation, similar to those in Crohn's disease (48%) and significantly higher than in the control group (P=0.01). Eleven of 12 patients (92%) with a mutation had initial chronic gut lesions vs. 15 of 42 patients (36%) with a wild type genotype (P=0.001). Carriers of CARD15 variants had a higher risk for evolution to ankylosing spondylitis (P=0.038). Evolution to clinical Crohn's disease was observed in 15% of patients with initial chronic inflammation.

Conclusion : CARD15 mutations clearly identify a subgroup of patients with spondyloarthropathy associated with chronic intestinal inflammation prone for evolution to Crohn's disease and ankylosing spondylitis.

A PROSPECTIVE ENDOSCOPIC STUDY OF CARDIAL INTESTINAL METAPLASIA. V. Muls, M. Nkuize, J. Dargent, A. Sarafidis, R. Ntounda, J. Mulkay, B. Caucheteur, H. Tibary, M. Buset. CHU St-Pierre, Brussels.

The incidence of adenocarcinoma of gastric cardia has increased in the last decade in United States and Western Europe. Cardia intestinal metaplasia (CIM) could be an intermediate step in the cascade of events leading to cancer.

Aim : To investigate the prevalence of CIM in patients undergoing upper gastro intestinal endoscopy in correlation with potential risk factors.

Methods : 232 patients were prospectively evaluated as to age, sex, race, tobacco, alcohol intake, NSAIDs and GERD. During endoscopy, four biopsies were taken from antrum and corpus according to the Sydney System, including helicobacter pylori (Hp) assessment by Giemsa staining. Two specimens were obtained from the gastric cardia.

Statistics : Chi-Square tests, Fisher's exact test and Crosstabulation.

Results : CIM was found in 38 (16.4 %), dysplasia in 8 patients, 6 mild, 2 moderate, always associated with CIM (3.4%). No correlation was found between CIM and sex (F=16.7% vs M=16.1%, NS), race (caucasien : 16.9% vs african : 12.0%, NS), alcohol intake (8.5% vs 18.4%, NS), NSAIDs (18.0% vs 15.8%, NS) or gastritis (13.7% vs 15.4%, NS). CIM was not more frequently found in Hp+ (17.1%) than in Hp- subjects (16.4%) (p=0.09). Statistical analysis shows a significantly higher prevalence of CIM in correlation with age (56.7 vs 47.4 yr, p=0.002), tobacco (25.3% vs 12.1%, p=0.01). The prevalence of CIM significantly rose according to the Savary-Miller classification of esophagitis (no esophagitis : 7.0%, grade 1 : 16.1%, grade 2 : 13.9%, grade 3 : 50.0%, grade 4 : 50.0%, p=0.003). There is a statistical correlation between CIM and the presence of IM in gastric antrum (44.4% vs 13.7%, p=0.003) or in Barrett esophagus (66.7% vs 12.9%, p<0.001).

Conclusions : This study shows a positive correlation between the presence of CIM and endoscopic features of GERD, and not with Hp prevalence. These results suggest a pathway, which may link GERD and the increasing incidence of cardiac cancer in developed countries. These findings support that multiple biopsy specimens from the cardiac mucosa should be obtained to detect early pathological changes in all patients with GERD. CIM also increases with age and smoking habits.

STUDY IN NAIVE CHRONIC HEPATITIS C PATIENTS COMPARING THREE DIFFERENT COMBINATION THERAPIES WITH INTERFERON a-2B (IFN) AND RIBAVIRIN : WEEKLY PEG-IFN VERSUS DAILY IFN VERSUS STANDARD REGIMEN OF IFN. Y. Horsmans (1), I. Colle (2), H. Van Vlierberghe (2), P. Langlet (3), M. Adler (4), R. Brenard (5), P. Michiels (6), N. Bourgeois (4), V. Lefebvre (7), J. Henrion (8), X. DeKoninck (9), L. Bruckers (10). (1) St Luc U.C.L. ; (2) UZ Gent ; (3) Brugmann ; (4) Erasme U.L.B. ; (5) Gilly ; (6) UZ Antwerpen ; (7) C.H.R. Namur ; (8) Jolimont ; (9) St-Pierre Ottignies ; (10) Diepenbeek.

The combination of PEG-interferon and ribavirin is considered to be the standard treatment for naive chronic HCV patients. A study was initiated to compare the sustained virological response and safety of daily IFN a-2b (Intron A®) versus Peginteron®, both in combination with Rebetol®. Naive chronic HCV patients were randomised in 3 groups with a ratio of 2 : 2 : 1. Group A : daily IFN (4 MIU s.c. for patients > 65 kg or 0.06 MIU/kg for patients < 65 kg) and ribavirin, group B : PEG-interferon a-2b (100 mg s.c. weekly for patients > 65 kg or 1.5 mg/kg weekly for patients < 65 kg) and ribavirin and group C (reference arm) : IFN a-2b (3 MUI s.c. TWI) and ribavirin. The duration of the treatment was 48 weeks for all 3 groups, with a 6 months follow-up period. 321 patients were enrolled : 128 in group A, 121 in group B and 72 in group C. Demographic data, PCR results and reasons for early withdrawal have been statistically analysed for 277 patients (44 patients are still on analysis). At baseline, the 3 groups didn't show any statistical difference regarding age, gender, race, genotype and METAVIR score. At the end of treatment, HCV RNA (Amplicor) was undetectable in 73% in group A, 72% in group B and 52% in group C. At week 24 of follow-up, the results were 71%, 57% and 40%, respectively. When comparing the efficacy of the daily IFN (+ ribavirin) and the PEG-IFN (+ ribavirin) regimen, no statistical difference was found ($p = 0.087$) even if a lower relapse rate was observed during the follow-up period in the daily arm. 142 patients withdrew before the termination of the treatment : 50 (47%) in group A, 53 (48%) in group B and 39 (65%) in group C. In group A, 36% of drop-outs were due to adverse events compared to 28% in group B and 3% in group C. In conclusion, daily weight based Intron A® dosing and PEG-Intron® weighed based dosing once weekly both in combination with ribavirin offer the same efficacy and safety rates even if the daily Intron A® (+ ribavirin) arm seems to induce less relapse in the follow-up period.

A POLYMORPHISM IN INSULIN-LIKE GROWTH FACTOR 1 GENE MAY BE ASSOCIATED WITH EARLY FISTULIZING BEHAVIOUR IN COLONIC CROHN'S DISEASE. N. Boussif (1), J. Belaiche (2), C. Libioulle (1), J. Thys (1), A. Vijverman (2), R. Winkler (1), F. El Yafi (2), M. Malaise (1), M. Georges (1), E. Louis (2). (1) GIGA, ULg ; (2) dept of Gastroenterology, CHU Liège.

Crohn's disease (CD) is a heterogeneous multifactorial polygenic disease. Beside genes involved in the pathogenesis of CD, other may influence its phenotype. Insulin-like Growth Factors (IGF) are involved in many phenomena potentially relevant to CD. Furthermore, increased expression of IGF1 and 2 has been consistently described in CD. Our aim was to study the association between several polymorphisms described in IGFs or IGF receptors (RIGF) and phenotypes of CD, essentially anatomic behaviour.

Methods : A 2 cohorts study was set up. Five polymorphisms in IGF1, IGF2, RIGF1 and RIGF2 were studied in a first cohort of 145 CD and 126 controls. Genotype frequencies were compared between CD and controls as well as between behaviours of CD defined according to Vienna classification determined at diagnosis and after 5 years. Positive results (with a $p < 0.1$) were then checked on a second cohort of 323 CD. A multivariate analysis was then performed including clinical and demographic variables potentially influencing CD behaviour.

Results : In the first cohort, there was no significant difference in genotypes frequencies between CD and controls as well as between various CD behaviours except for a functionally significant polymorphism, characterized by a variable number of a simple sequence repeat in the promoter of IGF1. Homozygotes for the most common allele (4/4), were significantly less frequent in penetrating (B3) than in structuring (B2) or uncomplicated (B1) behaviours both at diagnosis (26.5%, 65% and 42.1% ; $p = 0.045$) and after 5 years (23.3%, 56.5% and 51.6% ; $p = 0.034$). Such significant difference was not confirmed in the second cohort, but the trend mainly for disease behaviour 5 years after diagnosis was still present and the difference remained significant when grouping the two cohorts together. Multivariate analysis selected disease location and IGF1 genotype as independent parameter associated with CD behaviour at 5 years ($p < 0.001$), and when looking at genotypes in patients stratified for disease location, the lower frequency of 4/4 genotype in B3 patients was found essentially in colonic and ileocolonic disease.

Conclusion : An association seems to exist between this functionally significant polymorphism in the promoter of IGF1 gene and the inclination to develop early fistulizing disease, particularly in colonic CD.

THERAPEUTIC BENEFIT OF PPAR α -AGONIST PIOGLITAZONE ON HEPATIC FIBROSIS WHEN TREATMENT IS INITIATED EARLY IN THE COURSE OF CHRONIC LIVER INJURY. I. Leclercq, Ch. Sempoux, P. Stärkel, Y. Horsmans. Gastroenterology and Pathology Units, UCL, Brussels, Belgium.

Agonists of transcription factor peroxisome proliferator activated receptor α (PPAR α) prevent activation of hepatic stellate cells (HSC) and have been proposed as a therapeutic option for hepatic fibrosis. However, PPAR α expression is markedly decreased in activated HSC rendering them unresponsive to PPAR α stimulation. To test the effects of PPAR α agonist pioglitazone (PGZ) on established hepatic fibrosis, moderate (or severe) hepatic fibrosis was induced in Sprague Dawley rats by 2 (or 5) wks injection of carbon tetrachloride (CCl $_4$) or feeding a choline deficient (CD) diet. After the induction period, PGZ (0.1% food mixture) was given together with CCl $_4$ or CD diet for another 3 (or 6) weeks. Fibrosis was compared in rats treated or not with PGZ. After 2wks CCl $_4$, there was moderate peri-centrolobular fibrosis. After 5 wks, fibrosis severity increased with thick and complete centro-central septa. PGZ treatment, introduced after 2 wks of fibrosis induction, significantly reduced intrahepatic collagen deposit (thin and incomplete septa), hydroxyproline content (240 \pm 50 vs 316 \pm 84 μ g/g liver, p= 0.02) as well as the number of activated SMA positive HSC (7.9 \pm 2.3 vs 15.2 \pm 8.5%, p=0.045) to levels observed prior to the introduction of PGZ. Compared to CCl $_4$ alone, PGZ reduced the induction of regulator of matrix deposition chiefly produced by HSC such as collagen-I (9 \pm 2 vs 15 \pm 3.5, p= 0.04), TIMP-1 (0.7 \pm 0.2 vs 1.7 \pm 0.9, p<0.001) or TGF β 1 (7.3 \pm 1.8 vs 12.4 \pm 5.4, p=0.012). Importantly, PGZ did not modify necroinflammation as suggested by unaltered ALT or necroinflammatory scores of Ishak (5.9 \pm 2.4 vs 6.5 \pm 3.3). Similarly, fibrosis was reduced when PGZ was introduced after 2 wks of CD-diet compared with rats fed the CD diet alone (390 \pm 110 vs 525 \pm 144 μ g OH-proline/g liver p= 0.035 ; 3.6 \pm 1.4 vs 6.3 \pm 1.7 collagen mRNA, p=0.014). By contrast, PGZ failed to provide therapeutic protection when given after 5 wks CCl $_4$ or CD-diet, i.e. at an advanced stage of fibrosis progression. PGZ provides thus a therapeutic benefit on fibrosis progression in two models of chronic liver injury, but only when the treatment is initiated at early stages of fibrosis development. Our data are compatible with an inhibitory effect of PGZ on activation of quiescent HSC and, thereby, on the amplification of fibrogenesis.

TWO CANDIDATE BIOMARKERS TO MEASURE THE FUNCTIONALITY AND EFFECTIVITY OF PRE- AND PROBIOTICS IN HEALTHY VOLUNTEERS V. De Preter (1), T. Vanhoutte (2), K. Verbrugghe (3), L. De Vuyst (3), G. Huys (2), J. Swings (2), K. Verbeke(1). (1) Department of Gastrointestinal Research, University Hospital Gasthuisberg, K.U.Leuven. (2) Laboratory of Microbiology, Ghent University ; (3) Research Group of Industrial Microbiology, Fermentation Technology and Downstream Processing, VUBI, Belgium.

Introduction : Amongst the various claimed beneficial effects of pro- and prebiotics for the human host, it has been hypothesised that these types of functional foods are able to suppress the colonic generation and accumulation of potentially toxic protein fermentation metabolites, which is reflected in a lower urinary excretion of p-cresol and N-compounds. Direct evidence supporting this hypothesis is lacking mainly because of the unavailability of reliable biomarkers. In this study lactose-[15 N]-ureide and egg proteins, intrinsically labelled with [2 H $_4$]-tyrosine, were evaluated as potential biomarker candidates to test the functionality and effectivity of pre- and probiotics.

Methods : The effect of pro- and prebiotics on the colonic fate of these biomarkers was evaluated in a randomized, placebo-controlled, cross-over study with 19 healthy volunteers. At the start of the study and at the end of each 2-week study period, during which they were treated with either a probiotic (n=10, 6.5x10 9 *Lactobacillus casei* Shirota cells b.i.d.) or a prebiotic (n=9, lactulose 10 g b.i.d.), the healthy volunteer consumed a test meal containing the two biomarkers. Urine was collected in different fractions during 48 h and analysed for [15 N]-content by combustion-isotope ratio mass spectrometry and for p-[2 H $_4$]-cresol (a bacterial metabolite of 2 H $_4$ -tyrosine) by gas chromatography-mass spectrometry. Results were expressed in percentage of the administered dose.

Results : As compared with the placebo, the decrease in % dose p-[2 H $_4$]-cresol in the 24-48 h urine fraction was significantly higher after probiotic intake (p=0.042). Similar changes were observed for the 15 N tracer (p=0.016). After prebiotic intake, a significantly higher decrease in % dose p-[2 H $_4$]-cresol (p=0.005) in the 0-24 h urine fraction was found as compared to the placebo. Also a significantly more pronounced decrease in % dose 15 N excreted in the 6-24 h urine collection was found in comparison with the placebo intake period (p=0.029).

Conclusions : Our results demonstrate that suppression of the generation and accumulation of potentially toxic fermentation metabolites by pro- and prebiotics can reliably be monitored *in vivo* by the use of stable isotope labeled biomarkers.

RADIOLOGICAL SACROILIITIS, A HALLMARK OF SPONDYLITIS, IS LINKED WITH CARD15 GENE POLYMORPHISMS IN PATIENTS WITH CROHN'S DISEASE. H. Peeters (1), B. Vander Cruyssen (2), D. Laukens (3), P. Coucke (4), H. Mielants (2), F. De Keyser (2), M. De Vos (1). (1) Ghent University Hospital, Department of Gastroenterology ; (2) Department of Rheumatology ; (3) Ghent University, Department of Molecular Biomedical Research - VIB ; (4) Ghent University Hospital, Department of Human Genetics.

Objectives : Sacroiliitis is a common extra-intestinal manifestation of Crohn's disease (CD). In contrast to idiopathic ankylosing spondylitis (AS), its association with HLA-B27 phenotype is less evident. We investigated whether the presence of sacroiliitis in CD patients could be linked with the carriage of CARD15 polymorphisms.

Methods : One hundred and two consecutive CD patients were clinically evaluated by a rheumatologist. Radiographs of sacroiliac joints were performed and blindly assessed by 2 investigators. RFLP-PCR technique was used to genotype all patients for three single nucleotide polymorphisms (SNPs) in the CARD15 gene. Every SNP was verified by direct sequencing. HLA-B27 phenotype was determined.

Results : Radiological evidence of sacroiliitis with or without ankylosing spondylitis was found in 23 patients (23%). Only 13% were HLA-B27 positive. In contrast however, 78% of patients with sacroiliitis carried a CARD15 variant versus 48% of patients without sacroiliitis ($p=0.01$; OR 3.8, 95% CI : 1.3_11.5). Multivariate analysis (logistic regression) demonstrated that the association between sacroiliitis and CARD15 polymorphisms was independent from other CARD15 related phenotypes (ileal and fibrostenosing disease, young onset of disease and familial CD) ($p=0.036$).

Conclusions : We identified CARD15 variants as possible genetic markers for CD related sacroiliitis and found a first association between these polymorphisms and an extra-intestinal manifestation of CD.

HOW TO TREAT SEVERE PANCREATIC EXOCRINE INSUFFICIENCY? A PROSPECTIVE RANDOMIZED STUDY COMPARING HIGH DOSES OF PANCREATIC ENZYMES VERSUS STANDARD DOSES PLUS ESOMEPRAZOLE. P. Deprez (1), J.P. Da Silva Pinto (1), A. Geubel (1), Y. Horsmans (1), J.F. Gigot (2). (1) Dept of Gastroenterology, (2) Dept. of Digestive Surgery, Cliniques Universitaires St-Luc UCL, Brussels.

Aims : To evaluate patients with persistent steatorrhea under standard substitution with pancreatic enzymes, either due to chronic pancreatitis or to pancreatic surgery and to compare the efficacy of high doses of pancreatic enzymes (Creon Forte® 200 000 U/day) versus standard doses (Creon® 90 000 U/day) associated with the proton pump inhibitor esomeprazole (Nexiam® 40 mg/day).

Methods : patients were included in this prospective and randomized study if they had a persistent steatorrhea (>10 g fat/day) under standard doses of pancreatic enzymes. Dietary, nutritional and metabolic assessments (BMI, fat mass, TEE, basal metabolism), and measurement of exocrine pancreatic function (fecal elastase and stool fat) were performed at start point and after 4 to 6 weeks of treatment.

Results : 26 patients (14 M, 12 F), mean age 57 ± 13 years, were randomized, 11 in the high dose group (A) and 15 in the combination group (B). The 2 groups were well balanced concerning etiologies of exocrine insufficiency (50% chronic pancreatitis and 50% post-surgery) and severity of exocrine insufficiency. On basal state, significant percentages of patients were shown to have a low BMI (50%, mean 20 ± 3 kg/m²), a hypermetabolic status (23%, 1394 ± 246 kcal/day), an insufficient TEE (28%, 2475 ± 576 Kcal) with a correct nutrient repartition (lipid 37%, protein 15% and carbohydrate 46%). Exocrine pancreatic insufficiency was severe in all patients with a mean elastase level of 102 ± 21 ?g/g stool and a mean steatorrhea of 34 ± 19 g fat/day. During treatment, significant increases of TEE ($p<0.01$, 2475 ± 576 vs 2680 ± 429 Kcal) and decreases of fat mass ($p<0.05$, 23 ± 6 vs 17 ± 6 %) were observed in the 2 randomized groups, respectively. Significant improvement of steatorrhea ($p<0.05$, 28.8 ± 14.8 vs 20.0 ± 10.5 g fat/day) was however only observed in group B.

Conclusion : association of pancreatic enzymes with a potent proton pump inhibitor is significantly more efficient to treat severe steatorrhea in patients with advanced chronic pancreatitis and after pancreatic surgery, than increasing dosage of substitution enzymes.

CHEMOPREVENTION OF HEPATOCELLULAR CARCINOMA. ASSESSMENT OF THE EFFICACY OF PIOGLITAZONE AND LANREOTIDE IN A CARCINOGENIC RAT LIVER MODEL. I. Borbath (1), V. Lebrun (2), I. Leclercq (1), P. Moulin (2), Ch. Sempoux (2), Y. Horsmans (1). (1) Gastroenterology Unit ; (2) Pathology Unit, Cliniques Universitaires UCL-St-Luc, Brussels.

Background : Hepatocellular carcinoma (HCC) appears in more than 90% of cases on a cirrhotic liver. Albeit primary prevention seems efficient in some instances, few drugs have shown effect in secondary prevention. Both pioglitazone (PGZ) and lanreotide (LAN) have been shown to reduce proliferation of HCC cell lines.

Objectives : to analyse in a sequential two-stage carcinogenesis rat model the effect of PGZ and LAN on the development of preneoplastic cell foci.

Methods : Preneoplasia was induced in 15 male Wistar rats by 2 intra-peritoneal injections of the mutagen diethylnitrosamine (DEN), followed by 3 weeks of intra-gastric feeding with 2-acetylaminofluorene (AAF). Rats were divided into 3 groups. One group did not receive any drug (CTL group) ; the second (PGZ group) received PGZ 0.01% mixed with food, the third (LAN group) received LAN injections 3 mg/kg IM every 2 weeks. Immunohistochemistry was performed for the placental form of glutathione S-transferase (GSTp), marker of preneoplasia in the rat liver. Western Blotting was performed on liver homogenates to quantify GSTp as well as PCNA, Cyclin D1, CDK4 as markers of cell cycle entry. Apoptosis was assessed by determining caspase 3 activity using a fluorescence assay. Results were expressed as % of control set as 100% for Western Blot and as % of section surface labeling for immunohistochemistry.

Results : In immunohistochemistry, GSTp-labelled surface was decreased in PGZ group compared to CTL ($p=0.027$). GSTp area was also decreased in LAN group, but not significantly. Quantitation of GSTp protein by western blot confirmed these data in the PGZ group, with a decrease to 30% of CTL ($p=0.07$), but not in the LAN group, which showed a non significant increase to 226% of CTL. PCNA protein was significantly increased to 221% and 354% of CTL for PGZ and LAN respectively ($p=0.03$). Cyclin D1 protein was also increased, though not significantly, to 186% and 226% of CTL for PGZ and LAN respectively. Caspase 3 activity showed a non significant decrease in PIO and LAN group.

Conclusion : PGZ, in contrast to LAN, is active in reducing the size of preneoplastic foci in this model. The mechanisms of this action are not fully understood at the present time, but preliminary data show differential alteration of proliferation and apoptosis. Further analyses are required to determine the effect of PGZ and LAN on the balance of proliferation and apoptosis in preneoplastic foci and surrounding liver parenchyma.

DISCONTINUATION OF HEPATITIS B IMMUNOGLOBULINS IN LIVER TRANSPLANT PATIENTS IS POSSIBLE AFTER SUCCESSFUL VACCINATION WITH AN EXPERIMENTAL ANTI-HBV VACCINE. P. Stärkel, A. Bouvier, M. Stoffel, J. Lerut, Y. Horsmans. Department of Gastroenterology and Abdominal Surgery, Liver transplant program, St. Luc University Hospital, Brussels, Belgium and GSK, Rixensart, Belgium.

Background : Current strategies using lamivudine and hepatitis B immunoglobulins (HBIg) for prevention of hepatitis B re-infection after liver transplantation (LT) are expensive since treatment needs to be given on a life long basis.

Aim : To evaluate the possibility to discontinue HBIg prophylaxis after a reinforced course of hepatitis B vaccination using an experimental adjuvanted HbsAg/AS04 vaccine (GSK, Rixensart) in patients transplanted for hepatitis B.

Methods : 10 consecutive LT patients without evidence of HBV recurrence on HBIg monotherapy and stable low level immunosuppression (tacrolimus or cyclosporine monotherapy) were vaccinated with a double dose (left and right deltoid muscle, IM) of the vaccine at 0,1,2,6 and 12 months. HBIg were continued during baseline vaccination (0,1,2) and then only when anti-HBs titres determined every 6 weeks dropped below 150 IU/ml. Serum transaminases were followed before and 4 weeks after each injection of the vaccine. Anti-HBs titres were determined every 6 weeks. HBs antigen was checked every three months and HBV-DNA (branched DNA) was controlled at 0,3,6,12 and 18 months. Overall follow-up period was 18 months. Response to the vaccine was defined as an anti-HBs titre > 500 IU/ml 6 weeks after vaccination without prior administration of HBIg. Sustained long-term response was defined as anti-HBs titres > 500 IU/ml without further need for HBIg administration during a follow-up period of at least 12 months.

Results : Four out of ten patients (40%) developed a sustained long-term response (anti-HBs > 1000 IU/ml) and were completely free of HBIg at the end of the 18 months' follow-up period. Three patients had their HBIg requirements reduced by almost 40% during vaccination without, however, meeting the criteria for a sustained long-term response. Three patients did not respond to vaccination. No HBV recurrence, rejection episodes or side effects were seen in any of the patients during the 18 months of follow-up.

Conclusions : HBIg can be withdrawn in a substantial amount of patients following a reinforced course of HBV vaccination with vaccines containing new immuno-stimulating adjuvants. Vaccination with these new vaccines seems well tolerated and safe in LT patients. Vaccination schemes and doses need to be refined to further increase the response rates.

VIDEO CAPSULE ENDOSCOPY IN BELGIUM : A MULTICENTER REPORT. I. Demedts (1), A. Van Gossum (2), O. Dewit (3), M. Withofs (4), F. Mana (5), E. Louis (6), E. Macken (7), J. Belaiche (6), D. De Looze (4), P. Deprez (3), J. Devière (2), P. Pelckmans (7), P. Rutgeerts (1), D. Urbain (5). (1) Gasthuisberg, KUL ; (2) Erasme, ULB ; (3) St-Luc, UCL ; (4) UZ Gent ; (5) AZ VUB ; (6) CHU de Liège ; (7) UZ Antwerpen.

Video capsule endoscopy (VCE) is being used more frequently for the study of lesions in the small bowel.

Aim : To investigate the use of this new technique in clinical practice in Belgium.

Methods : all Belgian centers performing VCE (n=7) were contacted.

Results : all centers responded (total of 241 patients). M/F ratio was 119/122. Main indication for VCE was GI blood loss (either overt bleeding or iron deficient anemia) in 193 patients (80.1%), abdominal pain in 11 (4.6%), diarrhoea in 9 (3.7%) and other indications in 28 (11.6%). Most patients experienced symptoms for some time : 49.2% between 1 month and 1 year and an additional 30.3% for more than 1 year. This did not differ between bleeding (B) and non-bleeding (NB) indications. Overall mean age was 59 years (range : 5-87), however B patients were significantly older than NB (63 vs 46 y, p<0.0005). Significant findings were found in 159 of 241 patients (66%), this ratio was similar in B and NB patients. There was however a significant difference in the nature of the findings : in B there were significant more angiodysplastic lesions and fresh blood seen, and significantly less erosions or ulcers (see table).

	Bleeding	non bleeding	Chi-square
Fresh blood	38/129 29.5%	0/30	
Angiodysplasia	62/129 48.1%	2/30 6.7%	P <0,001
Erosion/ulcer	61/129 47.3%	22/30 73.3%	P <0.05
Polyp/tumor	12/129 9.3%	5/30 16.7%	NS
Other	23/129 17.8%	8/30 26.7%	NS

Summary : In Belgium, VCE is mainly used for the study of non-acute gastrointestinal blood loss. It carries an overall yield of 66%, and the nature of the findings differs on the indication for performing VCE.

Conclusion : VCE is a useful new technique at the disposal of gastroenterologists.

RAPID IMPROVEMENT OF BONE METABOLISM IN CROHN'S DISEASE AFTER INFLIXIMAB TREATMENT. V. Putzeys (1), N. Franchimont (2), J. Collette (3), S. Vermeire (4), P. Rutgeerts (4), M. De Vos (5), A. VanGossum (6), R. Fiasse (7), P. Pelckmans (8), M. Malaise (2), J. Belaiche (1), E. Louis (1). (1) Dept of Gastroenterology, CHU Liège ; (2) Dept of Rheumatology, CHU Liège ; (3) Dept of Bone metabolism, CHU Liège ; Depts of Gastroenterology, (4) Gasthuisberg, Leuven ; (5) UZ Gent ; (6) Hôpital Erasme Brussels ; (7) Saint-Luc, Brussels ; (8) AZ Antwerpen.

Background : Crohn's disease (CD) is associated with osteopenia and osteoporosis. Several factors affect bone metabolism in CD, including chronic inflammation, impaired calcium and Vit D absorption, and steroid treatment. Infliximab, which is able to induce a rapid clinical, biological and mucosal response, may influence these factors. We therefore assessed the evolution of bone metabolism in CD patients treated with infliximab.

Methods : We studied 71 CD patients treated for the first time with infliximab for either fistulizing (n=21) or non fistulizing (n=50) refractory CD. Biochemical markers of osteoformation (type-I procollagen N-terminal propeptide (PINP), bone alkaline phosphatase (BALP), osteocalcin (OSC)), and of osteoresorption (C-telopeptide of type-I collagen (CTx)), were measured in the serum before and 8 weeks after infliximab therapy (1 infusion in non fistulizing CD and 3 perfusions at weeks 0, 2, 6 in fistulizing CD). Serum levels of these markers were compared before and after treatment by a paired non parametric test. Demographic and clinical factors associated with clinically significant improvement of bone metabolism (increase of PINP >30% or decrease of CTx >30%) were looked for by univariate and multivariate analysis.

Results : Globally in the whole group of patients, there was a significant increase in serum concentration of osteoformation markers (BALP (ng/ml) : 7.3 (2.6-45.2) vs 8.2 (3.8-44.1), P=0.0008 ; PINP(ng/ml) : 30.3 (9-190) vs 41.8 (7.5-190), P=0.003 ; OSC (ng/ml) : 15.0 (0.9-75.3) vs 17.2 (0.3-57.5), P=0.001) and a significant reduction of osteoresorption marker (CTx (pg/ml) : 256.6 (15-1314) vs 224.3 (15-1765), P=0.04), 8 weeks after infliximab treatment. A clinically relevant increase in bone formation marker (PINP increase >30%) and a relevant decrease in bone resorption marker (CTx decrease >30%) were present in 46.0% and 38.2% of patients respectively (60.0% with at least one of these two results) and were not associated with any demographic or clinical factor tested.

Conclusion : Infliximab therapy in CD may influence bone metabolism by acting either on osteoformation or osteoresorption. A clinically relevant improvement in bone metabolism is present in 60.0% of the patients. This improvement seems to be independent of clinical response to infliximab, steroid weaning or other standard demographic or clinical data.

INVITED LECTURE

ARE BONE MARKERS USEFUL IN THE DIAGNOSIS OF IBD-RELATED OSTEOPOROSIS? R.W. Stockbrugger, University Hospital Maastricht, The Netherlands.

In Inflammatory Bowel Disease (IBD) bone mineral density (BMD) is measured by double X-ray absorptiometry (DXA). Osteoporosis is defined as a T-value of < -2.5 standard deviation of matched normal controls; its precursor osteopenia is defined by a T-value of -1.0 to -2.5 . Other imaging methods (MRI, X-ray, ultrasound) have been less reliable than DXA. There is a search for other methods to assess BMD, preferably non-invasive, e.g. in body fluids. The actual bone mass of a person is the point result of the osteoblastic and osteoclastic activities of cell populations deriving from progenitor osteocytes, continuously re-modelling the bone matrix. Osteoblast activity is reflected by serum osteocalcin (s-OC), whereas osteoclastic activity is reflected by serum type 1 carboxy-terminal telopeptide (s-1CTP), urinary pyridinoline (u-PYR) and deoxypyridinoline (u-DPD). In a multi-national, randomized intervention trial in ileo-coecal Crohn's disease (CD) comparing the effect of budesonide CIR with prednisolone (MATRIX study) osteoblastic and osteoclastic bone markers were measured before the start of the trial and during a follow-up of 24 months. At the start of the study, in 182 steroid-free (STF) patients with active disease increased osteoblastic action was counterbalanced by increased osteoclastic activity, whilst in 91 steroid-dependent patients (STD) with quiescent disease both osteoblastic and osteoclastic markers were within the normal range. In STF s-OC was negatively correlated to BMD ($P=0.025$), as was u-PYR in STD ($P=0.032$). During the 2-year follow-up, the achievement or maintenance of remission were correlated to normalisation of bone marker levels. Conclusion: In IBD bone markers reflect bone turnover rather than the individual BMD.

INFLUENCE OF ERYTHROMYCIN ON GASTRIC EMPTYING AND MEAL-RELATED. J. Arts, P. Caenepeel, K. Verbeke, J. Tack. University Hospitals KU Leuven, Belgium.

Although delayed gastric emptying is considered a major pathophysiological mechanism in functional dyspepsia, the efficacy of prokinetic drugs has not been established. Recent studies using macrolide prokinetics were negative, but receptor desensitisation may have played a role.

Aim: The present study was to evaluate the influence on meal-induced symptoms of acutely administered erythromycin in patients with gastroparesis.

Methods: In twenty patients with functional dyspepsia, gastric emptying was studied twice using the ^{14}C octanoic acid and ^{13}C glycin breath test to establish the reproducibility of the test. Breath samples were taken before the meal and at 15 minute intervals for a period of 240 minutes postprandially. At each breath sampling, the patient was asked to grade the intensity (0-3) of six dyspeptic symptoms. Twenty-four patients (3 men, mean age 43.5 ± 3 years,) with dyspeptic symptoms and delayed gastric emptying, were studied twice after pretreatment with saline or erythromycin i.v.

Results: Reproducibility was excellent in the first part of the study. During the first gastric emptying breath test, half emptying times for solids and liquids were 86 ± 7 and 67 ± 5 min respectively. The gastric emptying test with meal-related symptoms was repeated 63 ± 7 days later, at that moment half emptying times for solids and liquids were 90 ± 7 and 69 ± 5 min respectively. The Pearson's R value was 0.62 ($P=0.003$) and 0.66 ($P=0.002$) for solids and liquids respectively. The best reproducibility and lowest variability were found for the cumulative symptom score and the meal-related scores for fullness, bloating and pain. Pearson's value $R=0.78$ ($P<0.0001$) Treatment with erythromycin significantly enhanced solid and liquid gastric emptying ($t_{1/2}$ respectively 146 ± 27 vs. 72 ± 7 min, $p < 0.01$ and 87 ± 6 vs. 63 ± 5 min, $p < 0.001$). Only the severity of bloating was significantly improved by erythromycin (23 ± 3.9 vs. 14.5 ± 2.7 , $p < 0.01$); all other symptoms and the cumulative meal-related symptom score were not altered by erythromycin.

Conclusions: In a setting where desensitisation played no role, erythromycin enhanced gastric emptying was associated with only a modest effect on meal-related symptom severity.

ATYPICAL GORD IN BELGIUM : EPIDEMIOLOGY, CURRENT MANAGEMENT AND OPEN LABEL TREATMENT WITH ESOMEPRAZOLE 40 MG FOR ONE MONTH. E. Louis, P. Jorissen, B. Bastens, G. DHaens, N. Schoofs, A. Burette, P. Christiaens, J. Tack ; Study group of atypical GORD in Belgium.

The prevalence of atypical symptoms in patients suffering from GORD is not well known, and the optimal management of such symptoms has not been well established.

Aims : To set up an observatory of these atypical symptoms of GORD in Belgium and to study the efficacy of a one month treatment with esomeprazole 40 mg.

Patients and methods : Gastroenterologists participating in this observational survey were asked to register every new outpatient with symptoms of GORD during a period of 20 consecutive working days. All patients who reported predominant atypical manifestations of GORD were documented more in detail. Information was recorded about referral, previous and additional investigations, intensity and frequency of the atypical symptoms, and about previous and current therapeutic approaches. In patients with dominant chest pain or ENT symptoms, a treatment with Esomeprazole (Eso) 40 mg daily during 4 weeks was proposed.

Results : 90 gastroenterologists included 2864 patients consulting for symptoms suggestive of GORD, including 776 (27.1%) with dominant atypical symptoms (chest pain 38.9%, throat ache 29.5%, non-productive cough 19.3%, others 9.2%). There were no major demographic differences between GORD patients with dominant typical or atypical symptoms. Most of the patients with atypical GORD symptoms had a long-standing history (> 1 month in 81.7%, > 6 months in 37%), and daily symptoms (70.6%) of moderate intensity (63.5%). Endoscopy (in 2800 patients) showed significantly less oesophagitis, Barrett's oesophagus and hiatal hernia in atypical compared to typical GORD patients (respectively 68 vs. 81.1%, $p < 0.0001$; 1.6 vs. 3.7%, $p < 0.01$ and 43.4 vs. 49.8%, $p < 0.01$). Management of atypical GORD patients appeared to be very heterogeneous : a previous exploration and a previous treatment had been performed in 31.2% and 35.8% of the patients, respectively. The treatment choice of the gastroenterologist was standard dose PPI in 69.4%, double dose PPI in 14.2%, half dose PPI in 1.8%, H2-antagonist in 2.2%, prokinetics in 1.2%, others in 2.7% and no treatment in 8.5%. Overall 516/776 patients were included in the open phase of treatment with Eso 40 mg, but outcome data are only available in 228 patients. After one month, symptoms had disappeared in 57.1% and significantly improved in 26.6%.

Conclusion : Atypical GORD accounts for a large number of gastroenterology consultations in Belgium. It is associated with less endoscopic lesions than typical GORD. Its management is heterogeneous. Response rate after Eso 40 mg for one month was high (83.7%). (*support of AstraZeneca Belgium*).

PRESENTATION, DIAGNOSIS AND TREATMENT OF POST-FUNDOPLICATION DUMPING SYNDROME IN ADULTS. J. Arts, E. Roofthoof, P. Caenepeel, J. Tack. University Hospitals KULeuven.

Dumping after Nissen fundoplication has been reported in children (Ng DD et al), but not in adults. The underlying pathophysiology of dumping is complex.

Aim : The present study was to investigate the presence of post-Nissen dumping syndrome in adults, to determine the underlying pathophysiology and to evaluate the yield of a stepwise diagnostic and therapeutic approach.

Methods : Consecutive patients with symptoms suggestive of dumping syndrome (postprandial weakness, tremor, sweating, cramps, diarrhoea, reduced or loss of consciousness) after a Nissen fundoplication were evaluated prospectively. Symptoms, oral glucose tolerance testing, glycemia during symptoms, gastric emptying rate and accommodation of the proximal stomach were evaluated if available. Initial treatment consisted of diet, progressing to the glucose sequestrator acarbose, to the fundus-relaxing drug buspirone and the somatostatin analogue octreotide in case of persisting symptoms.

Results : 15 patients with presumed dumping after Nissen fundoplication were evaluated. Hypoglycaemia at the moment of symptoms (present in 6/11) and late hypoglycaemia during oral glucose load (in 6/11 patients) had the best diagnostic yield. The prevalence of fast liquid emptying (1/14) or of fast solid emptying (1/14) was unexpectedly low and, impaired fundic accommodation was found in 8/10. Diet with acarbose was given in 6 patients, 5 received the fundus-relaxing drug buspirone and 4 responded to octreotide. Two refractory patients had a surgical reintervention.

Conclusion : Dumping syndrome occurs after Nissen fundoplication in adults. Impaired accommodation seems to be a pathophysiological mechanism in a subset of patients. Therapeutic treatment remains difficult but a stepwise therapeutic approach is advisable.

COMPARATIVE EVALUATION OF THREE DIFFERENT BREATH TEST SUBSTRATES FOR ASSESSMENT OF OROCAECAL TRANSIT TIME IN HEALTHY VOLUNTEERS. V. De Preter, T. Coopmans, A. Luypaerts, K. Geboes, K. Verbeke. Dpt of Gastrointestinal Research, Gasthuisberg, KULeuven.

Introduction : Breath tests have been widely used for the evaluation of gastro-intestinal transit, often in combination with measurement of digestion. In the present study, gastric emptying (¹³C-octanoic acid) was measured simultaneously with orocaecal transit time (OCTT) using different substrates.

Methods : Fourteen healthy volunteers (7 men, 7 women ; mean age 21 years) were included in the study. On the day before to the test, unlabelled lactose ureide (1 g) was administered to stimulate the bacterial enzyme activity. After an overnight fast, 3 basal breath samples were taken before administration of the test meal containing 500 mg lactose-¹³C-ureide, 5 g Raftilin HP, 74 kBq inulin-¹⁴C-carboxylic acid to measure OCTT and 91 mg ¹³C-octanoic acid for measurement of gastric emptying. Breath samples were collected every 15 min. up to 10 hours. A sustained rise in hydrogen excretion of 10 ppm above baseline was defined as the cut-off value for OCTT. For the ^{13/14}CO₂ breath test, the OCTT was defined as the time at which a significant increase in ^{13/14}CO₂ from the background was seen in the breath, i.e. 2.5 times the standard deviation of all previous points above the running average of all previous points.

Results : A baseline separation between the gastric emptying and OCTT-¹³CO₂ excretion curve was obtained in all volunteers, allowing adequate calculation of gastric half emptying time (52 ± 21 min). An increase in H₂-excretion of 10 ppm was observed in 10 volunteers whereas an increase in ¹⁴CO₂ was found in 9 volunteers. 11 volunteers showed an increased ¹³CO₂ excretion because of LUR degradation. The OCTTs resulting from the three different substrates were 396 ± 108 min for lactose-¹³C-ureide, 398 ± 103 min for inulin-¹⁴C-carboxylic acid and 420 ± 61 min for Raftilin HP. Analysis of variance (ANOVA) and Tukey test for differences showed no significant differences.

Conclusions : This study demonstrated that gastric emptying time can be simultaneously assessed with the substrates used for OCTT and that lactose-¹³C-ureide, Raftilin HP and inulin-¹⁴C-carboxylic acid were equivalent substrates for the measurement of orocaecal transit time.

THE EFFECTIVENESS OF IMMUNOSUPPRESSION TO SUPPRESS THE FORMATION OF ANTIBODIES TO INFLIXIMAB IN CROHN'S DISEASE. M. Noman (1), S. Vermeire (1), G. Van Assche (1), F. Baert (2), G. D'Haens (3), J. Marcelletti (4), J. Do (4), K. Smith (4), P. Rutgeerts (1). (1) Dpt of Internal Medicine, Div. of Gastroenterology, University Hospital Gasthuisberg Leuven ; (2) Heilig Hart Ziekenhuis Roeselare ; (3) Imelda Ziekenhuis Bonheiden ; (4) Prometheus Laboratories Inc., San Diego, CA.

Background : Episodic infliximab treatment is associated with the formation of antibodies to infliximab (ATI) in up to 61% of patients which is clinically translated into infusion reactions and a reduced duration of response. Concomitant immunosuppression reduces the risk of ATI formation.

Aims : To investigate whether concomitant treatment with Methotrexate (MTX) and Azathioprine (Aza) are equally effective in reducing the risk of ATI formation.

Methods : A prospective multicenter study followed a cohort of 153 refractory patients treated with infliximab in an on demand schedule was prospectively followed. Patients were divided into 3 treatment groups : no immunosuppressives (n=59), and concomitant MTX (n=29), concomitant Aza (n=65). ATI and infliximab concentrations were determined before each infusion and 4 weeks after each infusion in a blinded fashion.

Results : Overall ATI were detected in 55% (85/153) of the patients while 23% (35/153) were ATI-negative. Despite episodic therapy 22% (33/153) had indeterminate levels, due to infliximab in the serum. The concomitant use of immunosuppressive therapy was associated with a lower incidence of ATI (45%) compared to patients not on a concomitant immunosuppressive (73% ; Chi square 18,5 ; df=2 ; p<0.001). This difference was observed when comparing both the MTX group (38% ATI ; Chi square 14,1 df=2 ; p<0.001) as well as the AZA group (48% ATI ; Chi square 17,2 ; df=2 ; p<0.001) with the group without immunosuppression. There was no difference however between Aza and MTX.

Conclusions : In this cohort concomitant immunosuppression reduced immunogenicity following infliximab treatment. No difference between MTX and Aza was observed.

	ATI positive	ATI negative	ATI indeterminate
MTX (n=29)	11 (38%)	9 (31%)	9 (31%)
Aza (n=65)	31 (48%)	23 (35%)	11 (17%)
No immunosuppression (n=59)	43 (73%)	3 (5%)	13 (22%)

GENOTYPE CC IN THE PROMOTER REGION OF APOPTOTIC GENE FAS LIGAND IS ASSOCIATED WITH BETTER CLINICAL RESPONSE TO INFLIXIMAB TREATMENT IN REFRACTORY LUMINAL CROHN'S DISEASE COMPARED TO TT GENOTYPE. T. Hlavaty, M. Pierik, S. Joossens, G. Claessens, N. Van Schuerbeek, P. Rutgeerts, S. Vermeire. University hospital Gasthuisberg Leuven.

Objective : Anti TNF α therapy with infliximab is effective in about 70% of patients with refractory luminal and fistulizing Crohns disease (CD). The effect of infliximab is ascribed to apoptosis of T cells. Clinical predictors do not fully explain the therapeutic outcome and genetic factors have been suggested. In this context we studied functional polymorphisms in genes of the apoptotic pathway as possible predictors to infliximab response.

Methods : A group of 240 patients treated with infliximab for refractory luminal Crohn's disease was genotyped for the functional Fas ligand C-843T, Apo-1/Fas promoter G-670A, MMP1 A-519G and MMP1 -1607 1G/2G polymorphisms using PCR RFLP method. Both clinical (using CDAI) and biological (using CRP) response were assessed at 4 weeks after the first infliximab infusion. Clinical data on sex, age at diagnosis and first infusion, localization and duration of disease, previous surgery and smoking were analyzed.

Results : Clinical response was observed in 70%, biological in 63% of patients. Carriage of the FAS ligand -843 T allele was associated with nonsignificant lower clinical response compared to C allele ($p=0,09$). Clinical response was observed in 73% of patients with CC genotype ($n=120$), in 67% with CT ($n=86$) and in 37% with TT genotype ($n=9$) being significant between CC and TT genotypes ($p=0,04$). Biological response expressed as the mean \pm CRP was $17,7\pm 35,8$ mg/L in CC genotype, $14,7\pm 27,8$ mg/L in CT genotype and $-7,5\pm 40,11$ mg/L in TT genotype group, being significant in CC vs. TT ($p=0.02$) and CT vs. TT ($p=0.01$) groups. There was no significant relationship between polymorphisms in other studied genes and response to infliximab therapy. Other identified predictors of clinical response in this cohort were colonic disease ($p=0,01$) and younger age ($p<0,05$). Predictor for biological response was higher initial CRP value ($p=0,04$).

Conclusion : In this cohort of CD patients, CC genotype in Fas ligand C-843T polymorphism was associated with better clinical response to infliximab in refractory luminal disease compared to TT genotype. This might be explained by recently described higher proapoptotic activity of CC genotype. Other functional polymorphisms in apoptotic pathway are currently being investigated.

CONCORDANCE OF SEROLOGIC AND GENETIC MARKERS IN TWINS WITH INFLAMMATORY BOWEL DISEASE. S. Joossens (1), M. Romberg-Camps (2), S. Vermeire (1), K. de Boer (3), G. Claessens (1), M. Russel (4), M. Pierik (1), N. Van Schuerbeek (1), R. Vlietinck (5), X. Bossuyt (1), P. Rutgeerts (1). (1) University Hospital Gasthuisberg Leuven ; (2) University Hospital Maastricht ; (3) VU Hospital Amsterdam ; (4) Medisch Spectrum Twente ; (5) Catholic University Leuven.

Background & Aims : Crohn's disease (CD) and ulcerative colitis (UC) are complex polygenic diseases of unknown origin. To determine whether genetic factors are implicated in the pathogenesis of serologic markers, we studied ASCA and pANCA in mono- and dizygotic twins with at least one member affected by IBD. The prevalence of CARD15 and TLR4 was also studied.

Methods : In total, 36 twin pairs were collected at two centers. The monozygotic twins ($n=14$) consisted of 14 CD, 6 UC and 8 unaffected. The dizygotic twins ($n=22$) included 18 CD, 5 UC, 2 indeterminate colitis (IC) and 19 unaffected. There were no mixed twin pairs (CD and UC). ASCA and pANCA were determined by a standardized ELISA and indirect immunofluorescence, respectively. Subjects were genotyped for TLR4 Asp299Gly and for the CARD15 variants Arg702Trp, Gly908Arg and Leu1007InsC using PCR-RFLP. Groups were compared using Chi-square test or Fisher's Exact.

Results : See Table. ASCA were found in 63% (20/32) of CD patients and in one, unaffected monozygotic sibling of CD. Only 3/72 (4.2%) subjects were pANCA positive : 1 UC patient and 2 unaffected siblings of UC patients. The prevalence of CARD15 was 38% (12/32) in CD patients, 27% (3/11) in UC patients and 22% (6/27) in unaffected siblings. For TLR4, the prevalence was 22% (7/32) in CD patients, 9% (1/11) in UC patients, 50% (1/2) in IC patients and 7% (2/27) in unaffected siblings.

Concordance in positive subgroup	monozygotic twins	dizygotic twins
Disease	43% (6/14)	14% (3/22)
ASCA+ ($p=0.015$)	57% (4/7)	0% (0/10)

Conclusions : Monozygotic twins are not only more concordant for disease, but also for ASCA. These results give additional evidence for a genetic basis of ASCA. Except for UC, the prevalence of CARD15 in this cohort was similar to previous reports. Numbers were too small to draw reliable conclusions for pANCA and TLR4 and therefore, collaborative efforts are needed for further investigation.

MAINTENANCE THERAPY FOR ULCERATIVE COLITIS HAS NO IMPACT ON CHANGES IN THE EXTENT OF ULCERATIVE COLITIS. M. De Vos, N. Eleftheriadis, G. Lambrecht, F. Baert, M. Cabooter, E. Louis MD, G. Van Assche, P. Schurmans, P. Caenepeel, M. Van Outryve, P. Lammens, A. Van Gossum, G. D'Haens. IBD Research Group.

Objectives : The aim of this study was to assess the potential role of maintenance therapy on the colonic extent of ulcerative colitis (UC).

Methods : A total of 98 patients, 56 males, 42 females, mean age 52 years, from 12 medical centers in Belgium, with an acute exacerbation of left-sided UC, were included. The colonic extent was determined by endoscopy at the time of initial diagnosis and at the actual flare-up. The mean UC duration was 93 ± 72 months. Active smoking was reported by 7% of patients. Sixty-six per cent of patients had quiescent disease during last year. The chi square-test was used for statistical analysis.

Results : Maintenance therapy in the last three months before the actual exacerbation was used by 69/98 (70%) of the patients. The most commonly used therapy were aminosalicylates (43%), while combined therapy with aminosalicylates, corticosteroids or immunosuppressives in all possible combinations was reported by 29.6% of patients. The extent of UC had not changed in 50.7% and 51.7% of patients, respectively with and without maintaining therapy (NS, $p=0,99$). Some degree of regression was observed in respectively 21.7% and 20.7% (NS, $p=0,99$), and some degree of extension in respectively 27.5% and 27.6% (NS, $p=0,99$). No relationship was found between changes in colonic extent and type of maintaining therapy, smoking habits or disease activity during the last year before the acute exacerbation.

Conclusions : According to this multicenter study, maintenance remission therapy for left-sided UC was not found to have significant effect on colonic extent. Further long-term studies are necessary to confirm these results.

EFFICACY AND SAFETY OF INFLIXIMAB IN CHILDREN WITH CROHN'S DISEASE : A SINGLE CENTER EXPERIENCE. V. Janssens (1), M. Bueno De Mesquita (1), G. Van Assche (2), P. Rutgeerts (2), I. Hoffman (1). (1) Dienst Kindergastroenterologie ; (2) Dienst Gastroenterologie, KULeuven.

Background : The advent of anti-TNF treatment in adult Crohn's disease (CD) and the increasing evidence for the role of TNF in the pathogenesis of childhood CD has led to increasing reports on the clinical use of infliximab in pediatrics, but experience is still limited. **Aim :** This study was to assess the efficacy and safety of infliximab treatment in a single center cohort of 19 children with CD.

Methods : Retrospective chart analysis of 19 pediatric CD patients (14 ?, 5?, age 13-18 yrs., mean 16.8 yrs) treated with infliximab over a period of 3 years for fistulizing disease (4/19) and/or luminal disease (15/19) in patients refractory to steroids and/or immune-suppression. Efficacy assessments including PCDAI, adverse events and concomitant medication use were retrospectively registered.

Results : Mean disease duration was 3.3 yrs (range 0-7) with a median cumulative number of 4 flares (range 1-8). A total of 120 infusions (5 mg/kg) were given (median 5/patient, range 1-23) at wk 0 (luminal disease) or 0,2,6 weeks (fistulizing disease) with on-demand episodic retreatment. Stable and ongoing concomitant medication included aminosalicylates in 18/19, steroids in 6/19 (previous steroid course in 19/19), azathioprine in 16/19 and methotrexate in 3/19 patients. All patients experienced clinical response after the first infusion (complete response in 9/19 and partial response in 10/19). The median PCDAI score was 32.5 (range 25-55) at wk0 and 10 (range 7.5-20) at wk4 (median change in PCDAI of 22.5). In the group with luminal disease, 13/15 responders relapsed and were episodically retreated with a mean response duration of 10.5 weeks. 2 patients lost response but regained response with a step-up dose of 10 mg/kg. In the fistulizing group 2/4 patients were episodically retreated with infliximab, but nevertheless had surgical intervention with continuation of infliximab after surgery. Steroids were tapered in all 6 patients within 4.5 months and none were restarted after infliximab. Contrary to previous reports the time to relapse was similar in patients with CD of recent onset (delay to diagnosis < 2 yrs, 10 wks) and in longstanding disease (delay > 2 yrs, 11 wks). Adverse events were reported by 5/19 patients. 4 had a moderate infusion reaction (one developed anti dsDNA Ab). 1 patient reported relapsing throat infections.

Conclusion : In our pediatric CD patient cohort infliximab was efficacious and well tolerated, but most patients needed episodic retreatment. The question remains whether the patients are better treated episodically or by infliximab maintenance 8 weekly.

GRANULOMAS, PATTERN RECOGNITION RECEPTORS (PRR) AND PHENOTYPES OF CROHN'S DISEASE (CD). M. Pierik (1), G. De Hertogh (2), S. Vermeire (1), S. Joossens (1), P. Van Eyken (2), G. Claessens (1), G. Van Assche (1), K. Geboes (2), P. Rutgeerts (1). (1) Department of Gastroenterology, University Hospital Gasthuisberg ; (2) Department of Morphology & Molecular Pathology, University Hospitals KULeuven.

Introduction : Granulomas represent a chronic immune response to persistent stimuli and are the histological hallmark of CD. Granulomas occur only in 15-36 % of biopsies and 50-60 % of surgical resections. A defective interaction between the gut bacterial flora and the innate immune response is hypothesised to play a key role in the pathogenesis of CD. This is underscored by the association between CD and polymorphisms CARD15 and TLR4. TLR4 and CARD15 are important PRR of the innate immune system that recognise bacterial lipopolysaccharide or muramyl dipeptide.

Methods & Aims : We wanted to assess genetic or phenotypic factors that determine granuloma formation in CD. From our database we collected 161 CD patients who underwent surgery. Fixed and fresh frozen biopsies from surgical resections were available for all patients. The presence or absence of granulomas was noted. Data about ASCA, indication for surgery (stenosis, fistula, perforation, refractory disease) gender and age, location of resection, duration of disease and smoking habits at the time of operation were collected. Patients were genotyped for the 3 SNPs in CARD15 associated with CD and Asp299Gly in TLR4. Uni- and multivariate analyses were performed (Statistica 6.0).

Results : The overall prevalence of granulomas in this cohort was 68.9%. We did not find any correlation between the presence of granulomas and TLR4 or CARD15 genotypes. The granuloma % increased however with more distal disease (55% ileum, 72% right colon, 88% left colon, 90% rectum, $p < 0.01$). Granulomas were also more frequent in patients who underwent surgery at a younger age ($p < 0.01$). Patients operated for stenosis had less granulomas compared to patients operated for fistula and perforation (59% and 76% respectively, $p = 0.03$).

Conclusion : In this large study of surgical resections of CD patients, granulomas were observed in 68.9%. We did not find an association between CARD15 or TLR4 polymorphisms and granulomas. A more intense immune response in young people may explain the association between age and granulomas. The finding that granulomas were more frequent in colon compared to ileal biopsies may be due to an over-activation of the adaptive immune system to the bacterial flora of the colon. The increasing prevalence of granulomas with more distal disease remains unexplained and further studies to define the pathogenesis of granulomas in CD are necessary.

A RETROSPECTIVE ENDOSCOPIC COHORT STUDY IN HIV+ PATIENTS BEFORE AND AFTER HAART. M. Nkuize, S. Dewit, V. Muls, R. Ntounda, J.P Mulkay, M. Buset. CHU Saint-Pierre, Brussels.

Background : Many previous studies indicate a decrease of opportunistic diseases among HIV+ patients since the use of highly active antiretroviral therapy (HAART) in 1995. AIM : To investigate the impact of HAART and CD4 lymphocytes cells counts (CD4) on gut opportunistic diseases, digestive symptoms, endoscopic findings and microbiology.

Methods : 553 HIV+ patients who underwent digestive endoscopy from 1/1991 to 12/1994 (pre HAART, group 1 : 279) and from 1/1999 to 12/2002 (post HAART, group 2 : 274) were retrospectively reviewed as to age, sex, opportunistic chemoprevention, antiretroviral therapy (non-HAART or HAART), CD4 cells counts, symptoms, diagnoses at the first upper gastrointestinal endoscopy or colonoscopy and microbiology.

Statistics : Fisher's exact test and chi-square test were used.

Results : We observed a statistically significant relative increase of female gender (44,89% vs 27,95% ; $p = 0,0004$), mean age (40 vs 37 yr ; $p = 0,003$), CD4 cell counts (306,52 vs 104,66 ; $P < 0,0001$), reflux symptoms (17,15% vs 5,73 ; $p = 0,00003$), GERD endoscopic features (26,27% vs 10,03 ; $p = 5,8 \cdot 10^{-7}$), inflammatory gastropathy (38,68% vs 23,65 ; $p = 0,0001$), gastric ulcer (8,39% vs 3,22% ; $p = 0,015$), and a significant decrease of the prevalence of esophageal mycosis (20,43% vs 35,84% ; $p = 0,0002$), diarrhea as the main symptom (12,66% vs 26,76% ; $p = 0,005$) and Kaposi's sarcoma (3,64% vs 9,67% ; $p = 0,02$). The prevalence of Helicobacter pylori increased (33,33% vs 10,92%), while both opportunist (4,01% vs 10,75%) and non opportunist infections (5,10% vs 16,63%) decreased. There was no significant modification of epigastric pain/dyspepsia as the clinical presentation, anal symptoms, abdominal pain/dyspepsia, and colitis, or anal pathology. The significant changes were correlated with an increase of CD4 cells count for esophageal Candida and Kaposi's sarcoma in group 2, abdominal pain in group 2, odynophagia/dysphagia in both group 1 and 2. These results are in favour of a correlation between the improvement of immunity due to more efficient antiviral therapy and the decrease of digestive diseases in AIDS, mostly, opportunistic infections and Kaposi's sarcoma.

RESTORATIVE PROCTOCOLECTOMY WITH ILEAL POUCH-ANAL ANASTOMOSIS : AVOIDING ILEOSTOMY BY RIGHT COLIC BORDERING ARCH PRESERVATION. D. Brandt (1), O. Dewit (2), J.F Colin (2), R. Detry (1), M. Melange (3), J. Jamart (4), A. Kartheuser (1). (1) Colorectal Surgery Unit - St-Luc University Hospital ; (2) Gastroenterology Dpt. St-Luc University Hospital ; (3) Gastroenterology Dpt. Mont-Godinne Univ. Hospital ; (4)Center of Biostatistics and Medical Documentation - Mont-Godinne Univ. Hospital.

Introduction : After restorative proctocolectomy (RPC) with endoanal mucosectomy, to perform an ileal pouch-anal anastomosis (IPAA) at the dentate line without any tension is a major cause of concern.

Objective : Systematic preservation of the right colic bordering arch (PRCBA) could provide sufficient mesenteric lengthening in order to achieve a tension-free pouch-anal anastomosis (IPAA) allowing omission of a protective ileostomy (PI).

Patients and Methods : 103 consecutive patients underwent (RPC) with IPAA for familial adenomatous polyposis (n = 40) or ulcerative colitis (n = 63). There were 35 women and 68 men [mean age : 33 y. (12-64)]. 31 patients have had a PRCBA without PI. The ileocolic artery (ICA) and/or the distal end of the superior mesenteric artery (SMA) have been systematically divided after PRCBA. For 25 patients, the intraoperative mesenteric lengthening has been measured. Mortality, intra and post-operative morbidity have been compared for 4 groups of patients : IPAA without PRCBA with PI (GI ; n = 62) ; IPAA without PRCBA without PI (GII ; n = 5) ; IPAA with PRCBA without PI (GIII ; n = 31) ; IPAA with PRCBA with PI (GIV ; n = 5).

Results : For GI and GII patients, IPAA has been performed under some degree of tension in all cases whereas for GIII and GIV patients, without any tension. Division of the distal SMA allowed mesenteric lengthening of 4.5 cm (range : 1.5-8.0) and division of the ICA, 3.5 cm (range : 1.5-6.0) with a mean total gain of 7.0 cm (range : 4.0-11.0). There were 2 cases of intraoperative pouch ischemia (1 GI, 1 GIV). There was no death. There were 9 general (6 GI, 1 GII, 1 GIII, 1 GIV) and 5 pelvic complications : 4 fistulas (1 GI, 3 GII, none for GIII and GIV) and 1 collection, none of them requiring surgery. After ileostomy closure, 1 patient had a bleeding and a patient had a small bowel injury requiring surgery.

Conclusions : PRCBA with division of one or two main mesenteric vascular pedicles provided sufficient mesenteric lengthening for tension-free IPAA allowing omission of the PI.

PROFILE OF SOLUBLE ACUTE-PHASE RESPONSES CYTOKINE-RECEPTORS IN CROHN'S DISEASE. T. Gustot (1), A. Lemmers (1), C. Nicaise (2), E. Quertinmont (3), S. Roland (1), A. Van Gossum (1), D. Franchimont (1), J. Devière (1). (1) Dept. of Gastroenterology, Erasme Hospital ; (2) Laboratory of Experimental Gastroenterology, ULB.

Introduction : The soluble cytokine receptors (sCR) modulate the *in vivo* activity of cytokines. Most of sCR behave as a cytokine-scavenger by inhibiting the binding of cytokines to their membrane receptors. Others, as sIL6R, potentiate the intracellular signal transduction of their ligands. Acute-Phase Response (APR) cytokines play a major role in Crohn's Disease (CD).

Aims : to study the systemic profile of APR sCR in CD and the modulation of these levels by both treatments (Infliximab and Corticosteroids) inducing disease's remission.

Methods : We prospectively investigated active CD patients (aCD) treated with Infliximab (n=21), with corticosteroids (n=10) and compared them with CD patients in clinical remission (rCD) (CDAI < 150 and normal CRP without immunosuppressants) (n=20) and healthy subjects (n=15). The circulating levels of TNF α , sTNFR1, sTNFR2, IL1b, sIL1RI, sIL1RII, IL6, sIL6R and sgp130 were measured using quantitative sandwich enzyme immunoassay at baseline, 1 and 4 weeks of treatment.

Results : Active CD compared to rCD and healthy subjects was associated with higher levels of sTNFR1 (p<0.05, p<0.01), sTNFR2 (p<0.01, p<0.01), sIL1RI (p<0.01, p<0.05), IL6 (p<0.01, p<0.01) and sIL6R (p<0.01, NS). In contrast, in the same group, lower levels of the soluble form of the IL1 'decoy' receptor, sIL1RII (p<0.05, p<0.01) and sgp130 (p<0.01, p<0.01) were found. They were significantly correlated with the CRP levels. Both Infliximab and steroid treatments induced a significant decrease of CRP and IL6 levels at 1 and 4 week. Interestingly, Infliximab decreases sTNFR2 level at 1 and 4 weeks (p<0.05) and enhanced the sIL6R level at 1 week (p<0.05). Corticosteroids increased sIL1RII at 1 week (p<0.05) and sIL1RI at 4 week (p<0.05).

Conclusion : Active CD is associated with major variations in sCR levels which may affect on the *in vivo* activity of cytokines and are differentially modulated by current therapies used for induction of remission. The sIL1RII and sgp130 represent potential future targets for the biological treatment of relapsing CD.

SYSTEMATIC MALONE'S APPENDICOSTOMY WITH TOTAL PERINEAL RECONSTRUCTION AFTER ABDOMINOPERINEAL RESECTION FOR RECTAL CANCER. E. Mael (1), Th. Van Wymersch (2), B. Crispin (3), O. Ykman (3), A. Kartheuser (3). (1) Colorectal Surgery Unit (2)Gastroenterology Dpt ; (3)Colorectal Surgery Unit and Colorectal cancer board - St-Luc University Hospital ; Brussels

Introduction : Defaecation disorders and faecal impaction after total perineal reconstruction (TPR) with double dynamic graciloplasty (DG) after abdomino-perineal resection (APR) for rectal cancer is a major cause of concern. In order to avoid these disorders after TPR, we have proposed the systematic adjunction of Malone's appendicostomy (MA) allowing antegrade colonic enema.

Objective : To evaluate morbidity, functional outcome and quality of life (QOL) after MA performed in combination with APR and TPR.

Patients and methods : Nine patients [6 females, 3 males ; mean age : 42 y.(range, 32-55)] underwent TPR with DG and MA after APR for rectal cancer. TPR and MA have been performed synchronously with APR in 8 cases and secondarily in 1 case. All patients had a temporary ileostomy. Stimulation device (Interstim©, Medtronic, Inc) has been placed during TA in 2 cases, secondarily in 6 cases. In 1 case, electrostimulation has been omitted because of pulmonary metastases. The EORTC QLQ-C30-CR38 has been used (with permission).

Results : There was no mortality. There were no complications related to the MA construction. Later, 1 patient had a MA stenosis requiring a plasty. One patient developed chronic MA discharge after a barium enema requiring anti-reflux valve revision. One patient required stimulation device explantation because of erosion of the tendon into the neorectum. No patient experienced MA catheterization problems. There was no episode of stool impaction nor colonic emptying disorders.

Conclusions : Our preliminary results of systematic adjunction of MA with TPR after APR for rectal cancer, seem to show that defaecation disorders could be avoided by antegrade colonic irrigation.

USE OF COMBINED INFLIXIMAB AND IV IRON SUCROSE IN REFRACTORY ANEMIA ASSOCIATED WITH CROHN'S DISEASE. EFFICACY AND SAFETY IN A SINGLE REFERRAL CENTER PATIENT COHORT. V. Van Hauwaert, L. Stremerch, G. Van Assche, S. Vermeire, P. Rutgeerts. Division of Gastroenterology, UZ Leuven.

Background : Infliximab treatment results in healing of mucosal ulcers and may therefore reduce intestinal iron loss and alleviate anemia in IBD.

Aim. To assess the role of concomitant infliximab therapy in Crohn's disease (CD) patients with refractory anemia treated with IV iron sucrose.

Methods : Retrospective chart analysis of 81 consecutive IBD patients treated with a first course of at least 600 mg IV iron sucrose (Venofer, Vifor, 200 mg/dose). 35 (43%) patients were concomitantly on infliximab 5 mg/kg in an episodic retreatment schedule and received their last dose no longer than 12 weeks before the first iron infusion. After a full course of Venofer, iron infusions were restarted when Hb levels decreased by 1 g/dl with low transferrin saturation levels.

Results : The infliximab and IBD control group were well balanced for age, gender, initial CRP and Hb levels and total iron sucrose dose, but not for concomitant immunosuppressives (infliximab : 91% vs. 36%, $p=1.2$ g/dL, NS). However, after a full course of IV iron, the time to the subsequent iron infusion was significantly longer in the infliximab group (see table). Disease activity assessed with CRP and CDAI was not affected by IV iron treatment. In total 521 infusions of 200 mg/kg IV iron were administered in the whole IBD group with interruption of iron treatment due to an infusion reaction in only 1/81. In 22 patients iron sucrose was infused immediately after infliximab (45 infusions) and well tolerated.

Conclusions : In our patient cohort infliximab per se did not ameliorate chronic anemia, but combined infliximab and IV iron sucrose therapy is safe and infliximab may prolong the effect of iron supplementation. Infliximab and iron sucrose can be successively administered with excellent tolerance.

	infliximab treated (n=35)	IBDcontrols (n=46)	P-value
Hemoglobine increase	0.92±1.3 (g/dL)	1.1±1.1	0.50
% patients reaching Hb 12.0 g/dL	31.4%	32.6%	0.90
Ferritin increase	80.1±59.6 (µg/L)	78.6±66.4	0.80
Transferrin saturation increase	11.2±14.5 (%)	7.4±8.6	0.19
Time to next iron infusion (mths.)	12.3±9.1	7.1±6.3	0.004

IGF1-R AND IGF1 ARE OVEREXPRESSED IN INTESTINAL STRICTURE OF CROHN'S DISEASE. F. El-Yafi (1), R. Winkler (2), N. Boussif (2), J. Belaiche (1), E. Louis (1). (1) Dept of Gastroenterology, CHU Liège ; (2) GIGA, ULg.

Aim of the study : Overexpression of IGF1 in Crohn's disease (CD) could play a role in intestinal strictures through its pro-fibrotic actions. We previously showed by immunohistochemistry that there is an altered expression of Type 1 IGF Receptor (IGF1-R) in the intestinal wall in CD. An increased number of inflammatory cells and fibroblasts express IGF1-R in CD, particularly in strictured intestine. The purpose of this study is to confirm this overexpression quantitatively.

Methods : RNA was extracted from transperietal intestinal surgical specimens from 5 patients with CD and 4 controls (operated for colonic adenocarcinoma) as well as total protein from 4 patients with CD. Semi-quantitative RT-PCR was performed in order to evaluate IGF1-R and IGF1 gene expression in normal intestine and CD. Protein expression of IGF1-R was carried out by immunoprecipitation of the total protein lysat followed by western blot both with an anti-IGF1-R antibody. BT-474, a cell line known to overexpress IGF1-R, was used as a positive control.

Results : IGF1-R and IGF1 mRNA were expressed in normal intestine and in Crohn's disease. This expression was globally lower in normal intestine, with some interindividual heterogeneity. In CD there was an overexpression of IGF1-R and IGF1 mRNA in strictured areas compared to uninflamed areas of the same patient in most cases (respectively 3/5 et 4/5). Moreover, in all patients with CD there was an overexpression of IGF1-R and/or its ligand IGF1 in strictured areas compared to the corresponding healthy area. As for IGF1-R protein, it was strongly expressed in all 4 patients with CD and this expression was higher in strictured areas in 3/4 patients.

Conclusion : IGF1-R and IGF1 overexpression, demonstrated in this study, may lead to an overactivation of IGF1-R in stricturing Crohn's disease. This overactivation of IGF1-R in inflammatory cells and fibroblasts could favour the development of intestinal fibrosis.

TREATMENT OF CROHN'S DISEASE WITH INFLIXIMAB IN CURRENT CLINICAL PRACTICE IN BELGIUM : A 4 YEARS MONOCENTRIC EXPERIENCE. E. Lebas, J. Belaiche, E. Louis. Gastroenterology, CHU Liège.

Infliximab has proved to be very effective and reasonably safe in controlled trials, for treating luminal or fistulizing refractory Crohn's disease (CD). Our aim was to assess the efficacy and safety of infliximab treatment in current practice in Belgium.

Methods : we performed a retrospective study on the patients treated with infliximab for CD in our department between 1/99 and 9/03. We looked at clinical and demographic characteristics of these patients, as well as at the short term and long term efficacy and tolerance to the drug.

Results : 59 CD patients were treated with infliximab in our dept. Indication was refractory luminal and fistulizing disease in 40.7% and 59.3%, respectively. When compared to the population of our other CD patients (n=445), these patients were more often smokers (55.9% vs 37.9% ; P=0.0008), had more colonic involvement (89.8% vs 54.1% ; P<0.0001), had more often fistulizing disease (59.3% vs 15.5% ; P<0.0001), and were more often treated with immunosuppressive drug (81.4% vs 24.7% ; P<0.0001). Response rate to first treatment was 88% (including 75% of complete response). CDAI dropped from 204 (77-355) to 118 (16-307) and CRP from 17 mg/l (3-142) to 3 mg/l (3-61). A positive response was associated to high CRP before treatment (P=0.005) and non-smoking (P=0.01). Tolerance was globally good but one patient developed a colonic occlusion 10 days after infusion and another experienced a non specific systemic reaction. The median duration of response was 4 months (0,3-20 months) and 20/29 patients could be weaned from steroids. 34 patients (57.6%) were subsequently retreated for a total of 136 reperusions (median of 4 retreatment : 1-11). Median interval between infusions in these patients was 7.6 months (2.6-39 months). One year after first treatment, 36/59 patients (61%) still benefit from the treatment (12 having not relapsed after first treatment and 24 being successfully retreated). There were 5 severe perfusion reactions necessitating to stop treatment (8.5%), 5 late dysimmune reactions (8.5%), and 3 infections necessitating hospitalisation. There was no case of cancer, lymphoma or tuberculosis and no death.

Conclusions : Efficacy and tolerance in this series are similar to the ones of published controlled trials. Non-smoking and elevated CRP before treatment were predictive of good clinical response. Sixty % of the patients experience long term benefit from infliximab treatment.

TREFOIL FACTOR 3 INCREASES MMP3 EXPRESSION IN INTESTINAL EPITHELIAL CELLS. J. Van Huysse (1), P. Demetter (1), I. Truyen (1), K. Vandembroucke (2), D. Laukens (2), L. Steidler (3), P. Rottiers (2), C. Cuvelier (1). (1) Ghent University Hospital, Dept of Pathology ; (2) Ghent University, Dept of Molecular Biomedical Research ; (3) University College Cork, Biosciences Institute.

Trefoil factor 3 (TFF3) is a member of the trefoil family of peptides, which are constitutively expressed in the gastrointestinal tract. Experiments using recombinant proteins in various animal models of gastric injury have demonstrated a role for TFF3 in repair processes. It enhances mucosal healing and restitution *in vivo* and promotes migration of intestinal epithelial cells *in vitro*. We have previously described a shedding of membranous E-cadherin using an in-vitro cell culture system with Caco-2 derived enterocytes after administration of recombinant mouse TFF3. The aim of this study was to investigate possible ways in which E-cadherin is shed. Enterocyte-like Caco-2 cells were treated with TFF3 during 2 hours. Total RNA was isolated and cDNA was synthesised. The cDNA probe was hybridised to the *Human Unigene Set 2* colony filters (RZPD), containing ~75.000 known and unknown EST's spotted in duplo. The *in vivo* induction of MMP3 by TFF3 was evaluated in the murine Dextran Sodium Sulfate (DSS)-induced model for acute colitis. During DSS administration, two groups of mice received daily inocula of LL-TFF3 or LL-pTREX1 (vector control) through an intragastric catheter. Mock-treated animals received daily 100 µl of BM9. Healthy control mice received normal drinking water throughout the experiment. MMP3 expression levels were evaluated in the colon at day 8 after treatment using quantitative PCR and immunohistochemistry. The macroarray results on the Caco-2 derived enterocytes showed a more than 2-fold increase in the expression of MMP3. In the mouse model, treatment with mTFF3 secreting *L. lactis*, LL-mTFF3 augmented the level of expression more than 10 times compared to the water controls, the relative expression levels of MMP3 were four times as high in the mock-treated mice suffering from acute colitis and administration of the vector control LL-pTREX1 led to a seven-fold increase. Immunohistochemical staining for MMP3 expression in these mice showed a significant increase in MMP3 expression in the crypt epithelium of the mice treated with LL-mTFF3.

Conclusion : We show that TFF3 administration leads to an increased MMP3 transcription and protein expression in intestinal epithelial cells. These data provide new insights into the working mechanism of trefoil factors and their protective capacities.

READ BY TITLE

GASTRIC EMPTYING IN NEWBORNS FED AN INTACT PROTEIN FORMULA, A PARTIALLY AND AN EXTENSIVELY HYDROLYSED FORMULA. S. Staelens (1), M. Van Den Driessche (2), D. Barclay (3), A. Carrie-Faessler (3), F. Haschke (3), K. Verbeke (4), K. Allegaert (5), B. Van Overmeire (6), M. Van Damme (1), G. Veereman-Wauters (1). (1) Queen Paola Childrens Hospital ; Nestle (2) Belgilux ; (3) Switzerland ; (4) Lab digestion and absorption KUL ; (5) NIC/ University Hospitals Leuven ; (6) NIC/University Hospital Antwerp.

Background : Gastric emptying (GE) is influenced by several nutritive and non-nutritive factors. Data are lacking about GE of various types of infant formulas.

Objectives : The first aim of this double blind randomized study was to assess GE in infants fed an intact protein formula (Beba start, Nestlé), a partially hydrolysed formula (Beba start HA, Nestlé) and an extensively hydrolysed formula (Experimental, Nestlé). The second aim was to compare GE values with reference values for emptying of breast milk (1).

Methods : Twenty healthy newborns (6 boys, 14 girls) were investigated, with parental consent. The infants had a mean gestational age of 37 wks (range 28-40 wks) and a birth weight of 2698 g (range 720-3690g). At enrollment, mean age was 4 wks 3 days (range 6 days-13 wks) and mean weight was 3466g (range 2100-5700g). The ¹³C-octanoic acid breath test (OAB) was used to assess GE of the 3 formulas with a 2-days interval. In addition a symptom diary was kept. Test meals were given after a fasting period of at least 3 hrs. Time sequence was : 2 basal breath samples, the feeding : one of the [¹³C]OA labeled infant formulas, a breath sample every 15 min during the next 4 hrs. Analysis of the expired ¹³C fraction was performed using isotope-ratio mass spectrometry and the GE curve and parameters : half emptying time (T_{1/2}) and gastric evacuation coefficient (GEC) were determined.

Results : The extensively hydrolysed formula emptied significantly faster than both the intact and partially hydrolysed formulas (Anova, < 0.05). There was no significant difference between GE of the partially hydrolysed and intact formula (Anova, p= 0.31). In comparison to GE of breastmilk in a different study group, the extensively hydrolysed formula emptied faster (13,6%), the partially hydrolysed and intact protein formula emptied slower (11,3% and 22%) but these values did not reach statistical significance. In these healthy infants, no differences in stool pattern, cramping and vomiting were recorded after receiving the various formulas.

Conclusions : In healthy infants, an extensively hydrolysed formula is evacuated from the stomach much more rapidly than a partial hydrolysate, an intact protein formula and even breastmilk. The potential therapeutic applications of this important feature remain to be studied in infants with feeding intolerance.

PREVALENCE AND CHARACTERISTICS OF DYSPEPTIC SYMPTOMS IN THE BELGIAN POPULATION. B. De Winter (1), H. Piessevaux (2), J. Tack (3), E. Louis (4), V. Muls (5), D. De Looze (6), P. Pelckmans (1), M. Deltenre (5), D. Urbain (7). Gastroenterology Dept (1) UZ Antwerpen ; (2) UCL St-Luc ; (3) KULeuven ; (4) Dept CHU Liège ; (5) ULB ; (6) UZ Gent ; (7) AZ VUB.

Most surveys in the general population did not adequately distinguish genuine dyspepsia (Dysp) from dyspepsia with co-existing reflux symptoms (Refl).

Aim : To investigate the prevalence and characteristics of Dysp with or without co-existing Refl in the Belgian population.

Methods : 26-items were addressed in a face to face interview collecting information on prevalence, presentation, use of health care resources, socio-economic and quality of life (QoL) impact, response to treatment of dyspeptic symptoms in a representative population sample. A four-item heartburn questionnaire was used to identify co-existing GERD (Johnson 1987).

Results : A cohort of 2025 subjects above 15 years of age was interviewed : 417 (20%) experienced stomach or digestion problems in the past 12 months : 222 (11 %) qualified as Dysp (Dysp+Refl-) alone, 148 (7%) had co-existing GERD (Dysp+Refl+), 43 (2%) had minimal symptoms (Dysp-Refl-) and 4 (0.2%) had reflux symptoms only (Dysp-Refl+). In the Dysp+Refl+ and Dysp+Refl- subjects, respectively 25 and 26 % reported symptoms' improvement after a bowel movement. Respectively 56 and 39 % of Dysp+Refl+ and Dysp+Refl- subjects reported to have symptoms at least once a week, vs. 21 % in the Dysp-Refl- group ($p<0.01$). Similarly, an impact on the daily QoL was found in 21% in Dysp+Refl+, in 18% in Dysp+Refl- and in 7% in Dysp-Refl-. Significantly more Dysp+Refl+ subjects (82%) seek medical advice compared to 53% of Dysp+Refl- subjects, leading to diagnostic procedure(s), mainly endoscopy, in 60 and 33% respectively. Among the Dysp-Refl- 40 % consulted a physician and 19% underwent at least an endoscopy. Significantly more Dysp+Refl+ than Dysp+Refl- subjects took medication (86 vs. 64%, $p<0.05$).

Conclusion : Dysp symptoms are very common in the general population in Belgium, impact negatively on QoL and lead to health care resources utilisation, even more so in the large subset of subjects having Refl symptoms. (*Sponsored by a grant of Astra Zeneca, Belgium*).

CLINICAL VALIDATION OF HIGH-RESOLUTION FAST SPIN ECHO MR COLONOGRAPHY AFTER COLON DISTENSION WITH AIR. D. Bielen, H. Bosmans, D. Vanbeckevoort, S. Tejpar, P. Rutgeerts, G. Marchal. University Hospital Gasthuisberg Leuven.

Purpose : We have evaluated a multishot T1 weighted 2D turbo spin echo sequence for MR colonography (MRC) after distension of the colon with air for its feasibility and ability to detect colonic polyps or tumours.

Materials and Methods : A randomly chosen patient population scheduled for conventional colonoscopy ($n=21$) was first submitted to MRC after classic bowel preparation with an electrolyte solution the same day. All patients were examined on a 1.5T Gyroscan system (Philips, Best, The Netherlands), using a multishot fast spin echo T1 weighted acquisition (T1wFSE) with a SENSE factor of 2. Images were acquired in both prone and supine position after the administration of a bowel relaxant. The degree of distension, amount of residual fluid and the delineation of the colonic wall were evaluated in different segments. Further the possibility for detection of polyps or other colonic lesions was evaluated.

Results and discussion : The T1wFSE technique provided excellent image sharpness in 19/21 subjects. In 17/21 patients residual fluid obscured the colonic wall in different segments, either in prone or supine position, especially in ascending colon and caecum. Distension was sufficient for diagnosis in all segments, at least in prone or supine position. These findings are consistent with those for CT colonography. One lesion > 10 mm was missed and none of the 4 smaller lesions were visualized. There was one false positive lesion. Missing lesions can be due to inconsistency in slice positions due to the multishot character of the MR technique. Residual fluid may have obscured especially the smaller lesions. Further shortcomings are the limited coverage and the signal drop-off at the borders of the field of view.

Conclusion : In order to make this MRC technique an alternative screening method for colonography, an improved patient preparation and a more practical acquisition technique should be worked out.

INCREASED EXPRESSION OF RECEPTOR ACTIVATOR OF NF-KB, ITS LIGAND RANKL AND A DECOY RECEPTOR, OSTEOPROTEGERIN, IN THE COLON OF CROHN'S DISEASE PATIENTS. C. Reenaers (1), N. Franchimont (2), C. Lambert (2), J. Belaiche (2), M. Malaise (2), V. Bours (2), P. Delvenne (2), E. Louis (1). (1)Dept of Gastroenterology, CHU Liège ; (2)GIGA, ULg.

Receptor activator of NF-kB (RANK) is mainly expressed by mature dendritic cells (DC). Together with its ligand RANKL, mainly expressed by T lymphocytes, it plays a critical role in DC-T lymphocytes interaction, particularly influencing T lymphocytes and DC survival as well as T cells activation. Osteoprotegerin (OPG), a decoy receptor for RANKL may interfere with this interaction. RANK, RANKL and OPG levels of expression have never been studied in the gut. Our aim was to check for mRNA expression of RANK, RANKL and OPG in human colon and to describe their protein expression in CD.

Material and methods : Total RNA was extracted from 5 normal colon samples from patients operated for colonic cancer. RANK, RANKL and OPG mRNA expression was studied by specific RT-PCR. Fixed colonic samples from 14 patients with CD and 4 controls were used to localize and quantify RANK expression by immunostaining and immunofluorescence. Supernatants of cultured colonic biopsies from 15 CD patients and 7 controls were analysed by immunoassays for RANKL and OPG production and their correlation to pro- and anti-inflammatory cytokines was studied.

Results : mRNA expression of RANK, RANKL and OPG was confirmed in human colon. RANK was mainly expressed in colonic mucosa by CD68+ activated macrophages and s100+ DC, as determined by immunostaining. The number of RANK+ cells was significantly increased in CD colon, particularly in inflamed area. Production of RANKL and OPG by cultured colonic biopsies was also significantly increased in CD. OPG production was significantly correlated to histological inflammation, pro- and anti-inflammatory cytokines while RANKL production was not significantly different between inflamed and uninfamed area.

Conclusion : RANK, RANKL and OPG are expressed in the human colon. RANK is mainly expressed by mucosal activated macrophages or DC and is overexpressed in CD. RANKL and OPG are also produced in larger amount by colonic mucosa in CD. The role of these molecules in the regulation of chronic intestinal inflammation is certainly worth investigating.

TOLERANCE OF LIVER TRANSPLANT RECIPIENTS TO STRENUOUS PHYSICAL ACTIVITY IN HIGH ALTITUDE. J. Pirenne (1), F. Nevens (1), F. Van Gelder (1), T. Kharkevitch (2), C. Verslype (1), E. Hamoir (3), W. Peetermans (1), B. Pirotte (4). (1) University Hospitals Leuven, Leuven, Belgium ; (2) UCB, Brussels, Belgium ; (3) University of Liège, Liège, Belgium ; (4) Free University of Brussels, Brussels, Belgium.

Quality of life and performance are altered by liver failure and improved by Liver Transplantation (LTx) but no study compares physical capacity in LTx versus normal healthy subjects. How LTx tolerate strenuous physical activity and extreme conditions (such as high altitude) is unknown.

Methods : 6 LTx patients participated to a trek up Kilimanjaro, Africa's highest point (5,895m). Inclusion criteria were : 1yr, normal liver/cardio/pulmonary function, normal life-pattern, non-sport-professional. LTx were accompanied by 15 control subjects (similar profile, matched for age/body-mass-index/gender/VO₂max). Daily data recording included : physical performance, Borg-scale, Lake Louise acute-mountain-sickness (AMS) score, cardiorespiratory parameters. Immunosuppression was steroid-free and tacrolimus-based (5-8ng/ml). Prevention against AMS and infection was given.

Results : 83.3% Tx subjects summited versus 84.6% controls (ns). No difference in Borg-scale was seen. Lake Louise score showed no increased vulnerability to AMS in LTx. O₂saturation (sat) decreased whereas arterial blood pressure and heart rate increased with increasing altitude in LTx and controls. The only difference was a higher arterial blood pressure at all time-points in LTx. One LTx with hepatitis C abandoned at 4,600m due to exhaustion, hypoglycemia, low O₂sat. A biopsy done immediately after the trek showed relapsing hepatitis that was clinically silent and compatible with normal activities at sea level but that impaired the liver adaptative response to exercise in altitude. No infection was seen among Tx subjects.

Conclusion : Selected LTx recipients, free of recurrent liver disease, tolerate extreme physical conditions (strenuous physical activities, extreme altitude) similarly to control subjects, suggesting that today's LTx technology has the potential to restore physical ability ad integrum.

IMPACT OF PREOPERATIVE SYSTEMIC CHEMOTHERAPY ON OPERATIVE RISK DURING LIVER RESECTION. W. Ngatchou, J.L. Van Laethem, C. Moreno, D. Van Gansbeke, B. Ickx, M. Gelin, V. Donckier. Hôpital Erasme, Brussels.

Background : The liver toxicity of systemic chemotherapy is well-recognised but its negative effect on liver surgery is poorly documented.

Aim of the study : To analyse the impact of preoperative chemotherapy on operative and postoperative evolution in patients undergoing liver resection.

Patients and methods : The operative and postoperative data of patients undergoing liver resection for malignant tumor were retrospectively reviewed. Patients with underlying chronic liver disease were excluded. Data were compared between the patients receiving chemotherapy within 6 months before liver resection (n= 39) (C+) and the patients without preoperative chemotherapy (n=24) (C-). Among these groups, data were separately analysed for patients undergoing major resection (resection of at least 3 liver segments) (MC+=21, MC-=18).

Results : Population data were identical in C- vs C+ and in MC- vs MC+ groups. There was no difference in the operative and postoperative mortality and morbidity in C- and C+ groups. In patients with major resection, perioperative blood loss were significantly increased in C+ as compared with C- (4816 ± 4563 ml vs 2518 ± 1250 , $p=0.04$), requiring more blood transfusions (MC+ : 5.4 ± 6 units vs MC- : 2.2 ± 2.4 , $p=0.04$). Postoperative morbidity and mortality were identical in C- vs C+ and in MC- vs MC+. The postoperative evolution of liver function was identical in C- vs C+. In patients with major resection, postoperative bilirubin levels tend to be higher in C+ patients (MC+ 6.7 ± 8.4 mg/dl vs MC- 2.8 ± 3 , $p=0.06$). Complications rates (including biliary fistula and stricture and sepsis) were identical in C- vs C+ and MC- vs MC+.

Conclusions : Neoadjuvant chemotherapy increases the operative risk and could worsen the early postoperative liver function in patients undergoing major liver resection. However, this has no significant impact on operative mortality and postoperative complications.

PRE-EXISTING DISEASE ACTIVITY DOES NOT INFLUENCE THE RESPONSE TO IV IRON SUCROSE THERAPY IN IBD PATIENTS. L. Stremersch, V. Van Hauwaert, G. Van Assche, S. Vermeire, P. Rutgeerts. Division of Gastroenterology, UZ Leuven.

Background : IV iron sucrose therapy is both safe and efficacious for refractory anemia in IBD. The role of ongoing disease activity in the response to IV iron is unclear and iron supplementation has been shown to aggravate disease in animal models of IBD.

Aim : To evaluate the role of disease activity in the response to IV iron sucrose therapy in a referral center cohort of IBD patients and to evaluate the safety and tolerability of IV iron in patients concomitantly treated with immunosuppressive and biological treatment.

Methods : Retrospective chart analysis of 81 IBD patients with a first course of at least 600 mg IV sucrose infusions (200mg, max 3x/wk) between Nov 1999 and Sep 2003. 30 non-IBD patients with digestive diseases served as a control population. Female patients were over-represented (IBD : 73%, non-IBD : 74%).

Results : A total of 649 iron sucrose infusions (200 mg IV) were given with a mean cumulative dose of 944 ± 392 mg per patient. The mean hemoglobine (Hb) change in all IBD patients was 1.1 ± 1.1 g/dL compared to 1.5 ± 1.6 g/dL ($P=0.1$) in non-IBD controls. The target Hb level of 12.0 g/dL was reached by 33% (IBD) and 27% (control) of patients. An initial hemoglobin level of 5 mg/L and >10 mg/L in 58 % and 38% of IBD patients respectively, but increased CRP was not associated with poor response (CRP > 5 mg/L : 1.0 ± 1.3 vs. 1.0 ± 1.2 g/dL, NS ; CRP > 10 mg/L : 1.1 ± 1.3 vs. 0.96 ± 1.3 g/dL, NS). Initial CDAI scores above >150 (active disease) were not associated with poor Hb response. On the contrary, CDAI scores positively related with response ($R=0.57$, $P=17.0$, NS). A moderate infusion-related reaction leading to interruption of treatment occurred in one out of 111 patients, but repeated infusions were well tolerated with only minor side effects in all other patients.

Conclusions : Pre-existent disease activity does not affect the response to IV iron sucrose in IBD patients with anemia confirming the importance of functional iron deficiency relative to iron store depletion. In our cohort tolerability was excellent and IV iron supplementation did not result in increased disease activity.

CRYPTOGENIC LIVER DISEASE : THE MAJOR CONTRIBUTION OF NON-ALCOHOLIC, NON OBESITY RELATED FATTY LIVER DISEASE. M. Adler (1), B. Vos (1), M. Gonzalez (1), N. Bourgeois (1), P. Thiry (2), N. Nagy (3). (1) Department of Gastroenterology ; (2) Department of Biochemistry ; (3) Department of Pathology, Hopital Erasme, ULB, Brussels.

The diagnostic yield of liver biopsy in patients with abnormal liver tests of unknown origin is poorly known. From November 1999 to April 2002, findings on 840 liver biopsies investigating persistently abnormal liver biochemistry from patients having either known liver disease (n = 792, 94%) or cryptogenic liver disease (n = 48, 5.7%) defined by the absence of any diagnostic feature using clinical (≤ 40 g alcoholic daily in men and ≤ 20 g daily in women, BMI < 25, no potential drug, vitamins or herbal hepatotoxicity), laboratory and imaging (no focal lesion at ultrasound, negative HBs Ag and HBc Ag immunocytochemistry on liver biopsy) investigations.

From the 48 patients with cryptogenic liver disease, histology demonstrated a normal liver in 17 (36%), non alcoholic (median alcohol intake : 60 g/week) fatty liver disease (NAFLD) in 15 (31%), cirrhosis in 5 and other diagnosis in 11. Steatosis alone was present in 8 patients, NASH in 3 (2 with fibrosis) and steatofibrosis in 4. Clinical and biochemical work-up performed after a mean (± SD) of 19 (± 11) months in 8 patients (5 males, 3 females) did not reveal (p > 0,1) any significant changes for the following indices (median, p2.5-97.5 % interquartiles) : BMI : 26.5 (24.1-31.4) vs 26.5 (25-28.8) kg/m², AST : 35 (22-99) vs 32 (19-59) IU, ALT : 45 (24-153) vs 47 (20-164) IU, gGT : 135 (39-303) vs 155 (46-388) IU, triglycerides : 135 (102-266) vs 149 (69-261) mg/dl, HDL : 53 (31-107) vs 58 (56-74) mg/dl, glycemia : 114 (100-137) vs 111 (89-157) mg/dl. Insulin-resistance measured in one of these lean subjects demonstrated severe alteration. Our study shows that cryptogenic liver disease represents 5.7% of the indications for liver biopsy and that, within this entity, primary (i.e. non alcoholic non obesity related) NAFLD represents the most frequent condition.

USE OF CHOLESTYRAMINE IN NON-COLLAGENOUS MICROSCOPIC COLITIS. D. Baert, M. Coppens, P. Burvenich, J. Lagae, K. Rasquin, E. Vanderstraeten, G. De Cock. AZ Maria Middelaers - St Jozef Gent.

Background : Chronic watery diarrhea is the main symptom of the microscopic colitis syndrome. In our institution, lymphocytic colitis (LC) and microscopic colitis not otherwise specified (NOS) are far more frequently diagnosed than collagenous colitis (CC). The goal of this study is to evaluate the antidiarrheal effect of cholestyramine, a bile acid binding agent, in non-collagenous microscopic colitis.

Study : The records of 13 patients with LC and 7 with NOS, who had received cholestyramine as first line therapy and who responded to a questionnaire, were reviewed. A CD3-staining was used to count the surface intra-epithelial lymphocytes per 100 epithelial nuclei.

Results : On an intention to treat basis, a good clinical effect of cholestyramine 3 x 4g/d was achieved in 75 % of the patients. There was no therapeutic effect in 15 % of the patients, who all had LC. In general, the antidiarrheal effect appeared within one week of treatment. On follow up, most of the responders were able to reduce the dose of cholestyramine to a median lowest effective dose of 4 to 8 g/d. However, none of them were able to stop their medication, with a median time of follow up of 2 years.

Conclusion : Cholestyramine provides a rapid and adequate symptomatic relief of the diarrhea in non-collagenous microscopic colitis. Unlike CC, NOS seems to respond equally well to cholestyramine as LC. If there is no beneficial effect within one week, it is advisable to switch to another therapy. In the group of responders, the dosage can usually be reduced, but not stopped for a long period of time.

COMPUTED TOMOGRAPHIC COLONOGRAPHY AND COLONOSCOPY : TWO COMPLEMENTARY MEANS OF INVESTIGATION? A. Badaoui (1), D. Salovic (2), J. Gallez (1), N. Hachez (1), S. Noirhomme (1), N. Akle (1), J. Kirsch (2), A. Nakad (1). (1) Clinique Notre Dame - Gastroenterology - Tournai ; (2) Clinique Notre Dame - Radiology – Tournai.

Aim : Colonoscopy and computed tomographic colonography (CTC) require a vigorous preparation. If CTC gives rise to suspect a lesion or in case of an incomplete colonoscopy, it should be possible to perform both investigations with less than 24 hours so as to benefit from a shared preparation. We studied the feasibility of this course of action.

Patients and methods : On a total of 500 colonoscopies and 60 CTCs performed over a period of 6 months, 47 patients benefited from having both investigations performed within 24 hours, with the same preparation. Twenty-three patients (4,6%) with incomplete colonoscopies benefited from a subsequent CTC because of neoplastic stenosis (3), non-passable sigmoid (5), and dolichocolon (15). Twenty-four CTCs (40%) required a colonoscopy because of discovery of polyps (16), suspicious colon segments (insufficient distension) (5) and non-contributory investigations (intolerance, residues...)(3).

Results : The second investigation was at all times possible and contributory in all patients without requiring a second preparation. Three out of the 16 polyps revealed during CTC (having a diameter of 5, 6, and 14 mm) were not objectified by colonoscopy (18,7%). Two out of the 5 suspicious segments described during CTC were normal in colonoscopy. The remaining 3 were compatible with benign inflammatory pathologies.

Conclusion : Pending on a good collaboration between radiologists, endoscopists and anesthetists, colonoscopy and CTC can be complementary, and can be performed using the same preparation within 24 hours. The association of these two methods can enhance the sensitivity of CTC and reduce colonoscopy-linked morbidity in case of an incomplete colonoscopy or when lesions are suspected during CTC.

THE INDUCTION OF ANTINUCLEAR ANTIBODIES FOLLOWING INFLIXIMAB TREATMENT IS NOT RELATED TO PROFOUND CRP DOWN REGULATION. S. Vermeire, M. Noman, G. Van Assche, T. Hlavaty, P. Rutgeerts. UZ Gasthuisberg, Dpt of Gastroenterology.

Background & Aims : Infliximab treatment leads to the formation of antinuclear antibodies (ANA) in up to 50% of patients and is associated with the female gender and with skin manifestations. The mechanism of ANA induction is not known but cannot be explained by Antibody Dependent Cell-Mediated Cytotoxicity (ADCC) and cell lysis alone. In mice, serum amyloid P (SAP), the analogue of C Reactive Protein (CRP) in humans, controls the clearance of chromatin and of auto-immune symptoms. SAP^{-/-} mice spontaneously develop signs of auto-immunity and lupus. We therefore hypothesised that profound down regulation of CRP following infliximab is responsible for induction of ANA.

Methods : A cohort of 125 CD patients treated with infliximab in an expanded access program were previously studied for ANA (*Gastroenterology* 2003 ;125 :32-9). CRP (mg/L) was available for all patients before and 4 weeks after each infliximab infusion and was correlated to the time of induction of ANA.

Results : Following infliximab, there were 70/125 (56%) patients who developed ANA. Most patients developed ANA+ already after first infusion and >80% converted to ANA+ after 3 infusions. The difference in CRP between 4 weeks after infusion and the level before infusion (DCRP, median) did not differ between ANA- (DCRP 8.75) and ANA+ patients (DCRP 8). DCRP in patients developing ANA early after first infusion (DCRP 5.1) did not differ from DCRP in patients developing ANA at later time points (D9.95) (t-test 0.71). Within patients, the DCRP at ANA induction was not different from the DCRP before ANA induction. The majority of patients (114/125) showed increased CRP. Only 11 patients had no elevated CRP at baseline (4 fistulizing disease) and 8 of them still developed ANA. Finally, when ANA and CRP were correlated to clinical response to infliximab, no differences were observed.

Conclusion : The occurrence of ANA following infliximab treatment cannot be explained by down regulation of C Reactive protein. The exact mechanism of ANA induction remains unknown.

TOLL-LIKE RECEPTOR (TLR)-4 ASP299GLY, INFLAMMATION AND RESPONSE TO INFLIXIMAB IN CROHN'S DISEASE (CD). M. Pierik, T. Hlavaty, G. Claessens, N. Van Schuerbeek, S. Joossens, P. Rutgeerts, S. Vermeire. Department of Gastroenterology, University Hospital Gasthuisberg, Leuven.

Introduction : CD is a chronic inflammatory disorder. An excessive immune response to the intestinal bacterial flora, plays a role in the pathogenesis of the disease. This is underscored by the association between CARD15 and TLR-4 polymorphisms and CD. Binding of lipopolysaccharide (LPS) of Gram negative bacteria to TLR4 results via the NF- κ B signalling pathway in the transcription of many inflammatory genes among which TNF-alpha. The functional Asp299Gly polymorphism in TLR4 impairs the efficacy of LPS signalling. Chimeric monoclonal antibodies against TNF-alpha (Infliximab) are a very effective treatment for CD, however 20-30% of patients are refractory. It has been shown that patients with more inflammation at baseline (as defined by high CRP levels) respond better to Infliximab.

Methods & aims : We studied the effect of TLR4 Asp299Gly on inflammation and both the biological and clinical response to Infliximab. 300 CD patients were collected in a prospective trial to evaluate response to Infliximab. Patients received Infliximab in an on demand schedule. CRP and CDAI were evaluated before infusion and at week 4 or 10 following Infliximab (for luminal and fistulising disease respectively). Clinical response and remission were defined as a decrease of CDAI of 100 points and a drop below 150 points. Biological response and remission as a 50% decrease of CRP levels and drop below 3 mg/L respectively. Genotyping was done by PCR RFLP. Groups were compared using Chi-square test and t-test.

Results : There was no difference in CRP levels at baseline between patients with and without TLR4 mutations. Median decrease in CDAI and CRP was 97 points (IQR 35,5-206) and 7.4 mg/l (IQR 0-23,6). A clinical response was seen in 65% of the patients and 49% of these entered clinical remission. Biological response and remission were seen in 69% and 37% of the patients respectively. We did not find a significant difference in response to Infliximab treatment between patients with (16%) and without the TLR4 Asp299Gly rare allele (84%).

Conclusion : Although the functional TLR4 Asp299Gly polymorphism results in less translocation of NF- κ B upon stimulation with LPS, we did not find a association between this SNP and both clinical and biological response to Infliximab in CD. Similar results have been obtained for CARD15 and suggest that innate immunity genes do not seem to influence response to Infliximab.

LAPAROSCOPIC ILEAL POUCH-ANAL ANASTOMOSIS WITHOUT ILEOSTOMY : PRELIMINARY RESULTS. L. Charre (1), J. Kayser (2), D. Brandt (1), M. Mourad (1), C. Faber (2), A. Kartheuser (1). (1) Colorectal Surgery Unit - St-Luc University Hospital ; (2) Dpt of Surgery – Clin. Sainte-Thérèse –Luxembourg.

Introduction : Laparoscopic restorative proctocolectomy (RPC) with ileal pouch-anal anastomosis (IPAA) has already been reported for ulcerative colitis (UC) and for familial adenomatous polyposis (FAP). We have chosen to perform laparoscopic RPC with Riolan's arcade preservation (RAP) and IPAA at the dental line without ileostomy as previously described for open surgery.

Objective : The aim of this study was to compare morbidity, mortality and late functional results of laparoscopic RPC, RAP and IPAA with open surgery.

Patients and Methods : Twelve patients underwent a laparoscopic RPC with IPAA from march 2001 to march 2003 (LS). They were compared with 12 patients who underwent an open RPC with IPAA from February 2000 to March 2003 (OS). The two groups were similar for age (LS : 35.2 \pm 3.6 ; OS : 32.3 \pm 2.7), sex (9 women, 3 men in each group), body mass index (BMI) (LS : 24.4 \pm 1.6 ; OS : 24.4 \pm 0.9), and pathology (LS : 8 UC, 4 FAP ; OS : 9 UC, 3 FAP). The mean follow-up was respectively 13.9 \pm 3.8 and 22.6 \pm 2.6 months for LS and OS.

Results : Riolan arcade was respectively preserved in 9/12 and 11/12 patients in OS and LS groups (ns). Three patients of OS group underwent an ileostomy and one in LS group. There was no conversion in LS group. Two patients in the OS group had a complication (one dehydration, one ascitis infection in a patient with liver transplant) and three patients in the LS had a complication (one pre-sacral collection, one portal thrombosis and one wound abscess). There were no mortality in either group. Length of hospitalization was 14.2 \pm 2 days in OS group versus 15.5 \pm 1.8 days in LS group (ns). Eleven patients in each group had a normal fecal continence (Wexner score - OS group : 2.8 \pm 0.7 ; LS group : 2.8 \pm 0.8). Number of daily stools, use of antidiarrheal drugs, fecal continence and diet were not statistically different. Sexual and urinary functions were normal for all patients. Quality of life was similar in both groups (SF36 score in OS group : 0.78 \pm 0.05 versus 0.77 \pm 0.04 in LS group ; ns).

Conclusion : Our preliminary results suggest that it is possible to perform all the specific technical steps of an open RCP with IPAA and RAP by laparoscopy. The functional result of the laparoscopic technique seem to be at least equivalent to open surgery.

STUDY OF SOMATOSTATIN LEVELS DURING THE EVOLUTION OF A SCHISTOSOMIASIS INFECTION IN LOW AND HIGH PATHOLOGY MICE. K. Van de Vijver (1), K. Kuypers (1), I. Depoortere (2), T. Peeters (2), J. Weyler (3), W. Jacobs (1), S. Chatterjee (1), E. Van Marck (1). (1) Labo Anatomopathologie, Universiteit Antwerpen, Wilrijk ; (2) Labo Gastro-intestinale Hormonen, O&N, K.U.Leuven-Gasthuisberg, Leuven ; (3) Epidemiologie en Sociale Geneeskunde, Universiteit Antwerpen, Wilrijk.

Background & Aims. Schistosomiasis is a helminthic disease causing considerable morbidity and mortality worldwide due to fibrotic liver complications. The neuropeptide somatostatin exerts an antifibrotic effect on the hepatic stellate cells in vitro, and reduces fibrosis and morbidity in *Schistosoma mansoni*-infected animals. It is the drug of choice to control variceal bleeding and reduce portal pressure. The aim of the present study was to investigate the role of somatostatin in the evolution of *S. mansoni*-caused disease severity in two inbred mice strains, C57BL/6J (low pathology) and C3H/HeN (high pathology).

Methods. 40 C57BL/6J and 40 C3H/HeN mice were infected with 30 cercariae and sacrificed after 8 weeks (acute stage of infection) or after 16 weeks (chronic stage of infection) post-infection (p.i.). For each group 5 controls were included. Plasma samples were taken by cardiac puncture and the somatostatin levels were determined. The degree of liver pathology was examined quantitatively by egg count, measurement of granuloma volume and determination of hepatic hydroxyproline as a value for hepatic fibrosis.

Results. The C3H/HeN-strain showed a more severe pathology with significantly larger granulomas, more hepatic fibrosis and a higher mortality than the C57BL/6J-strain. Within each strain the mice had significantly more hepatic fibrosis in the chronic stage of the infection as compared to the acute stage. Somatostatin levels in the plasma of the C57BL/6J-strain rose significantly at 16 weeks p.i. (controls 146.00 ± 12.96 ng/ml vs infected 275.62 ± 23.48 ng/ml ; $p=0.004$), whereas no difference could be noticed at 8 weeks p.i. (controls 160.80 ± 17.24 ng/ml vs infected 191.53 ± 12.56 ng/ml ; $p=0.238$). In the C3H/HeN-strain higher somatostatin concentrations were found at 8 weeks p.i. (controls 160.40 ± 15.12 ng/ml vs infected 204.94 ± 7.85 ng/ml ; $p=0.023$) but not at 16 weeks p.i. (controls 191.20 ± 15.43 ng/ml vs 260.30 ± 29.49 ng/ml ; $p=0.142$).

Discussion. Somatostatin levels in the plasma may play a regulatory role determining the progression to severe or low pathology during *S. mansoni* infection. During the evolution of the infection somatostatin increases in the 'low pathology' C57BL/6J-mouse. C3H/HeN-mice only show an increase in somatostatin at 8 weeks, whereas in the chronic stage, when liver pathology worsens and mortality increases, the levels of this neuropeptide are not elevated.

DOES HELICOBACTER PYLORI INFLUENCE LIVER HISTOLOGY IN PATIENTS WITH CHRONIC HEPATITIS C? S. Bakari (1), P. Langlet (1), L. Lasser (1), E.M. Talib (1), C. Deprez (2), E. De Koster (1). (1) Dept Gastroenterology CHU Brugmann ; (2) Dept Pathology CHU Brugmann.

Aim : It was shown in the past that HCV-infected patients with liver cirrhosis (J Hepatol. 2000 ;33 :648-50) and with chronic HCV-related hepatitis (New Microbiol. 2003 ;26 :321-8) have a higher HP seroprevalence than age-matched blood donors. We wondered whether in HCV-infected patients present HP gastric infection might modulate liver histology and liver function tests.

Patients and methods : We detected the current presence of HP using Urea Breath Test in 38 consecutive HCV infected patients (26 male, 12 female, age 49.7 y \pm 14 [22-76]) who underwent liver biopsy for evaluation of the indication of antiviral treatment. 7 patients used >60 g alcohol/d. Activity and fibrosis were evaluated using the Metavir-score (0-4).

Results : All patients had chronic HCV hepatitis ; 7 had HCV-related cirrhosis. HP was present in 20 pts (13 M, 7 F) and absent in 18 (13 M, 5 F). None of the following were different in HP positive vs negative patients : age, gender, alcohol use, smoking, drug abuse, ASAT, ALAT, bilirubin, gamma-GT, alkaline phosphatase, WBC, hemoglobin, platelets. HP positive patients had a significantly higher fibrosis score (2.52 vs 2.05, Kruskal-Wallis $p=0.04$), and more often had cirrhosis (HP pos 6/18, HP neg 1/20, Fisher's exact $p = 0.04$).

Conclusions : In this small series, the current presence of HP was associated with an increased risk of liver fibrosis and cirrhosis in HCV infected patients. Although this does not prove causality, it raises the question whether HP is a risk factor for progression of HCV-related liver disease through fibrosis to cirrhosis (which should be investigated using a multivariate analysis in a large patient sample), and whether HP eradication might influence the outcome of HCV-related liver disease.

GASTRIC EMPTYING FOR LIQUIDS AS MEASURED BY USING ^{13}C -ACETATE BREATH TEST : COMPARISON WITH THE $^{99\text{mTc}}$ COLLOIDS SCINTIGRAPHY. F. Mana (1), R. Jacobs (1), P. Franken (2), F. Lindenburg (1), D. Urbain (1). (1) AZ VUB Dpt. of Gastroenterology Brussels, Belgium ; (2) AZ VUB Nuclear Medicine Brussels, Belgium.

The classical method using $^{99\text{mTc}}$ colloids is not always usable due to the radiation (children, pregnancy) or the inability to move the patient to the Nuclear Medicine Unit like in the case of patients hospitalised in ICU in whom a gastric emptying should be evaluated before starting liquid enteral feeding. Therefore, breath tests using ^{13}C -substrates are interesting alternatives.

Aim : Our study was to evaluate the ^{13}C -Acetate method in healthy volunteers, to compare the results with the reference method, based on scintigraphy and to establish normal values.

Methods : twenty healthy volunteers (M/F = 1, age 24-27 years) were included in the study. The gastric emptying rate of a double-labelled test meal was measured simultaneously by scintigraphy using 20 mBq $^{99\text{mTc}}$ colloids and by ^{13}C -Acetate breath test using 150 mg ^{13}C -Acetate. Scintigraphy consisted in anterior and posterior images acquisition every 5 minutes during the first hour and every 15 minutes during the second hour. Concerning the ^{13}C -Acetate breath test, breath samples were collected every 5 minutes during the first hour and every 10 minutes during the following 3 hours. The results were expressed as the time in minutes needed to obtain 50 % excretion of the ingested ^{13}C dosis, and as half emptying time in minutes for the scintigraphy. Differences between values were assessed by the paired two tails t test. For correlations, the Spearman correlation test was used.

Results : t 1/2 was respectively 33.87 min \pm 11.73 for $^{99\text{mTc}}$ and 97.10 min \pm 12.14 for ^{13}C -Acetate. A significant correlation was observed between results obtained by both methods (r = 0.52) in the same patients. Using $^{99\text{mTc}}$, t 1/2 was respectively 28 min \pm 8.21 in males and 39.35 \pm 12.14 in females (P = 0.027). This gender related difference was not observed with the ^{13}C -Acetate. Calculated normal values (95 % interval of confidence) for $^{99\text{mTc}}$ were respectively 22-30 min for males and 34-48 min for females. Concerning ^{13}C -Acetate normal values were 88-109 minutes.

Conclusion : the ^{13}C -Acetate breath test can be used for clinical purpose as alternative to the classical radio-isotopic method, particularly in patients in whom the classical method cannot be performed. Using the $^{99\text{mTc}}$ colloids scintigraphy, a faster gastric emptying for liquids was observed in males. With the ^{13}C -Acetate method, no gender related differences could be observed. The study also allowed to obtain normal values for both methods in healthy volunteers.

INFLIXIMAB THERAPY IS ASSOCIATED WITH EARLY INCREASE IN LYMPHOCYTOSIS IRRESPECTIVE OF THE CLINICAL OR BIOLOGICAL RESPONSE. S. Vermeire, M. Noman, G. Van Assche, T. Hlavaty, M. Bueno de Mesquita, P. Rutgeerts. University Hospital Leuven.

Introduction & Aim : In Crohn's disease migration of activated lymphocytes to the bowel is an important pathogenic mechanism. Blockade of migration may be an important mechanism of action of infliximab. We investigated whether the baseline lymphocyte count is a predictive factor for response to infliximab and whether blockade of migration of lymphocytes correlates with efficacy of the drug.

Methods : We measured lymphocyte counts, CRP and CDAI at baseline and 4 weeks after infusion of infliximab 5mg/kg in 125 patients with refractory Crohn's disease. We studied the relationship between change in lymphocytes and clinical (CDAI) and biological response (CRP).

Results : At baseline there was no relationship between lymphocyte counts and CDAI or CRP. At 4 weeks 95 patients (75%) responded to infliximab. Lymphocyte counts increased significantly in the total cohort with 26% (from 1,285 \pm 660 at baseline to 1,616 \pm 827 at 4 weeks, p<0.0001). In responders the increase (307 \pm 770 ; 23%) was similar to the increase seen in non-responders (373 \pm 630 ; 30%). In patients with elevated CRP at baseline the clinical response (DCDAI) was also not related to the increase in lymphocyte count.

Conclusion : Infliximab treatment is associated with a significant increase in absolute lymphocyte count at 4 weeks after infusion. This can be explained by a decrease in migration of lymphocytes as a consequence of downregulation of adhesion molecules. However, the increase in lymphocyte count was in our study not related to the clinical response nor to the biological response to infliximab. These data suggest that blockade of homing of T-lymphocytes is not a key mechanism of action of infliximab. Baseline lymphocyte counts are not a predictor for response to infliximab and the increase in lymphocyte counts under therapy cannot be used as a surrogate marker for response to infliximab.

LUMINAL CONTACT IMPROVES HUMAN SMALL BOWEL PRESERVATION. A. DeRoover, L. de Leval, J. Gilmaire, O. Detry, C. Coimbra, J. Boniver, P. Honoré, M. Meurisse. Departments of Transplantation and Pathology, Centre Hospitalier Universitaire, Liège, Belgium.

Aim. In clinical conditions small bowel is preserved without any contact between the mucosa and the preservation solution. We evaluated the impact of a luminal contact with different preservation solutions on the structural quality of small bowel preservation.

M&M. Segments of ileum were harvested from stable multi-organ donors and flushed with UW. For each donor, ileal segments were placed in UW without any contact between the mucosa and the preservation solution, as in clinical conditions (control group). Adjacent segments were cut on their antimesenteric side and placed in UW, UW+glutamine, Celsior or NaCl 0.9% so that their mucosa was widely in touch with the solution. The grafts were preserved in ice and removed from the preservation fluid at different time intervals (0, 3, 6 and 12 hours). Tissues were studied by optical microscopy after H&E staining of formalin-fixed paraffin-embedded specimens. A median histological score was attributed after examination of 3 random slides for each ileal segment per time point and compared between groups of the same donor.

Results. As early as after 3 hours of preservation, detachment of the villi epithelium is observed in the control group. Preservation in this group during 6 and 12 hours is accompanied by further tissue alteration with complete detachment of the epithelium from the basal membrane of the villi. The histological score of the segments preserved with a luminal contact with UW, UW+glutamine and Celsior was always significantly higher than its control from the same donor. Contact of the lumen with NaCl 0.9% was associated with early severe oedema and villus destruction.

Conclusion. Luminal contact between the mucosa of intestinal grafts and an adapted preservation solution improves the quality of small bowel preservation in the human. Addition of substrates to the solution can have further beneficial impact while the absence of impermeants in the solution can have a detrimental effect.

A TDT STUDY OF NOVEL POLYMORPHISMS IN THE INNATE IMMUNITY GENES TOLL LIKE RECEPTOR (TLR) 2 AND 4 IN INFLAMMATORY BOWEL DISEASE (IBD). M. Pierik, G. Claessens, N. Van Schuerbeek, S. Joossens, P. Rutgeerts, S. Vermeire. Department of Gastroenterology, University Hospital Gasthuisberg, Leuven, Belgium.

Introduction : The important role of innate immunity receptors in the pathogenesis of IBD is underscored by the confirmed association between 3 CARD15 variants and CD and also by the recent association between Asp299Gly in TLR4 and IBD. TLR2 is highly homologous to TLR4 and also recognises bacterial lipopolysaccharide (LPS). To our knowledge, the TLR2 gene has not been studied in IBD.

Methods : Public databases were screened for single nucleotide polymorphisms (SNPs) in the TLR2 and TLR4 genes. Only non-synonymous SNPs located in coding sequences and one SNP in the 3'UTR were selected. DNA from 215 IBD-affected trios (CD 159, UC 49 and IC 7) was amplified for C1892A, G2258A, A7484T, A1736G in TLR2 and for A5827G, A4102G, A4564T, A4738G, A5318G, A4959G in TLR4 using PCR-RFLP. Mutant allele frequencies were calculated using founders only. TDT and haplo-TDT were performed using Genehunter 2.1.

Results : Only 3 SNPs in TLR2 had allele frequencies of more than 1% (4% for 1892A, 3.3% for 2258A and 5.1% for 7484T). All studied SNPs in TLR4 had minor allele frequencies of less than 1%. TDT showed a clear overtransmission of 7484A allele in TLR2 towards affected offspring in the total cohort (T/U 32/10 Chi 11.52, $p < 0.001$) and in CD only (T/U 24/9, Chi 6.82, $p = 0.009$). When combining, C1892A and G2258A, A7484T only the haplotype CGA was significantly overtransmitted towards affected offspring in both IBD and CD (both $p < 0.01$).

Conclusion : In this study, we have validated 3 novel SNPs in TLR2 in a Caucasian population. Furthermore, by studying these SNPs in a cohort of IBD patients, a significant distortion of transmission for TLR2 A7484T was observed. This provides further evidence that the innate immunity pathway is important in the genetic susceptibility of IBD and the data should therefore be validated by functional studies.

LAPAROSCOPIC SIGMOIDECTOMY FOR FISTULIZED DIVERTICULITIS. S. Laurent, B. Detroz, O. Detry, M. Meurisse, P. Honoré. Dpt of Abdominal Surgery, CHU Sart Tilman, Liège.

Background : Nowadays colo-rectal laparoscopic surgery has shown its advantages in terms of reduced post-operative pain, earlier recovery of intestinal peristalsis and shorter hospital stay. Few studies reported results of laparoscopic surgery in complicated diverticulitis. The aim of this study was to analyze the results of laparoscopic sigmoidectomy in patients with fistulized sigmoiditis.

Methods : The authors retrospectively reviewed 16 patients operated on for fistulized sigmoidectomy between 1992 and 2003, in a series of 247 laparoscopic colectomies. Eleven patients presented with colo-vesical fistula, 4 with colovaginal and one with colo-cutaneous fistula, and all were caused by sigmoiditis. The procedure always consisted in coelioscopic sigmoidectomy with stapled transanal suture and eventually closure of the cystic or vaginal orifice.

Results : Mean age was 60 years (range : 39 to 78 years). Mean number of diverticulitis crises before operation was 3 (range : 1 to 5). Mean time between the last crisis and operation was 46 weeks (range : 2 to 250 weeks). Three cases (18.7%) were converted in the three first years of experience. Reason to conversion was necessary intestinal resection, splenectomy and wound of anterior rectum. The mean operating time was 172 min (range : 100 to 280 min). Mean hospitalization stay was 5.7 days (3-12 days). Mortality rate was 0%. Postoperative morbidity (12.5%) consisted in one pulmonary infection and one splenectomy. Long-term follow-up demonstrated no diverticulitis recurrence and one incisional hernia.

Conclusion : In experienced hands, laparoscopic sigmoidectomy may be a safe and effective procedure for fistulized sigmoiditis.

CAPSULE ENDOSCOPY EXAMINATION OF PATIENTS WITH OBSCURE GASTROINTESTINAL BLEEDING : EVALUATION OF THE CLINICAL IMPACT. C. Moreno, M. Arvanitakis, J. Devière, A. Van Gossum. Dpt of Gastroenterology, Erasme University Hospital.

Background : Capsule Endoscopy (CE) has been reported to contribute to the diagnostic management of patients with obscure gastrointestinal bleeding (OGB). Nevertheless, clinical outcome data is lacking. The aim of our study was to determine the clinical outcome of patients undergoing CE for investigation of OGB.

Methods : 38 patients who were referred to our department for investigation of OGB and who underwent a CE examination (M2A Given Imaging) were included in this study. Patients, by definition, had had previous endoscopies (upper gastrointestinal endoscopy and colonoscopy) that had failed to identify a bleeding source. A questionnaire was sent to the referring doctors 4 to 26 months after the capsule investigation. The following items were investigated : the final diagnosis of OGB, the treatment applied and the clinical outcome.

Results : Data was recorded for 26 patients out of 38 (17F, 9M). The mean age was 63 years (range, 21-84). *Positive findings* : a positive finding, defined as a possible cause of OGB observed during CE, was noted in 10 patients (Diagnostic yield=38,5%). Findings included small bowel lesions in 6 cases and gastroduodenal lesions in 4 cases. As a result of the capsule investigation, specific therapy was administered in 8 patients (surgery=2, endoscopic=2, medical=4). Six of the 8 patients treated had no further anemia. Amongst the two patients who had no treatment, one deceased and the other was considered inapt for surgery because of heart failure. Final diagnosis of OGB, based on surgery findings or complementary endoscopy or small bowel XR studies, was in accord with positive findings of CE in all these 10 patients. *Negative findings* : Amongst the 16 patients with a negative CE, 10 had a digestive lesion (3 small bowel lesions, based on surgery or small bowel XR studies) as a final diagnosis.

Conclusion : Despite the relatively low diagnostic yield of 38,5%, patients with a positive result at CE had further intervention in 80% and were successfully treated in 60% of cases. We had no false positive results in this study, which suggests a high positive predictive value of CE of 100%.

LIMITED INFLUENCES OF CHEMOTHERAPY ON HEALTHY AND METASTATIC LIVER PARENCHYMA FROM COLORECTAL CANCER. N. Van Damme (1), P. Demetter (2), W. De Bock (1), B. de Hemptinne (3), M. Praet (2), M. Peeters (1). (1) Ghent University Hospital Department of Gastroenterology ; (2) Department of Pathology ; (3) Department of Surgery.

Background : Liver metastasis often occurs in patients who undergo surgical removal of the primary colorectal tumour. The adhesion molecules, E-cadherin/catenin complex, are closely involved in the development and growth of metastatic tumours. Today, no data are available on the effect of chemotherapy on liver parenchyma.

Patients and methods : Thirty-nine patients (27 males and 12 females, with a mean age of 60.3 years) who underwent liver resection for hepatic metastasis from colorectal cancer were included in the study. Tissue samples taken from the tumour and surrounding liver parenchyma were immunohistochemically stained for E-cadherin, a -, b -, and g -catenin, VEGF and p53. The patients were divided in two groups : those (n=15) who had no chemotherapy for at least 6 months before the liver resections and those (n=24) who were treated with chemotherapy before liver resections. A score from 0 to 3 was given for the number of positive cells and from 0 to 3 for the intensity of staining in these cells, in both healthy and metastatic liver parenchyma. The sum of both scores, with a maximum of 6, was made. Changes were statistically evaluated with the Mann-Whitney U test.

Results : In the non-involved liver parenchyma no differences could be observed for E-cadherin/catenin complex, VEGF and p53 between patients receiving or not receiving chemotherapy. VEGF expression was more pronounced in metastatic liver parenchyma from patients receiving chemotherapy in comparison with patients receiving no chemotherapy (p=0.048). There were no differences for the E-cadherin/catenin complex.

Discussion : No histochemical changes are observed in non-involved liver parenchyma. A limited influence of chemotherapy was noticed on metastatic liver parenchyma.

ROUTINE MICROSATELLITE INSTABILITY TESTING IN SPORADIC COLORECTAL TUMOURS. N. Van Damme (1), P. Demetter (2), K. Claes (3), B. Poppe (3), F. Baert (5), J. Roelens (4), A. De Paepe (3), C. Cuvelier (2), M. Peeters (1). Ghent University Hospital (1) Dpt of Gastroenterology ; (2) Dpt of Pathology ; (3) Center for Medical Genetics ; (4) Heilig Hart Ziekenhuis Roeselare

Background : Microsatellite instability (MSI) due to defective mismatch repair genes has been reported in the majority of colorectal tumours from patients with hereditary non polyposis colorectal cancer syndrome and in 10 to 15% of unselected sporadic colorectal cancers. The identification of cancers associated with MSI requires classical molecular testing as the golden standard.

Aim : To test microsatellite instability (MSI) in sporadic colorectal cancer from two centers.

Patients and methods : Colorectal cancers from 68 non-selected patients [Ghent University Hospital (n=42) and Heilig Hart Ziekenhuis Roeselare (n=26)] were assessed for DNA mismatch repair deficiency by MSI testing at 5 loci (BAT25, BAT26, D2S123, D5S346, D17S250). MSI-high (MSI-h) was defined as instability at 2 or more of the 5 loci tested, and MSI-low (MSI-l) was defined as instability at 1 to 3 of the loci tested.

Results : High MSI was found in five tumours (7.35%) and low MSI in two tumours (2.94%) ; 61 tumours (89.71%) were microsatellite stable. Remarkable, four of the 26 patients (15.38%) from Heilig Hart Ziekenhuis Roeselare were MSI-h while only one of the 42 patients (2.38%) from Ghent University Hospital had a MSI-h phenotype. The results of hMLH-1 and hMSH-2 immunohistochemistry detection will be available at the time of the congress. Correlation with MSI-status will be performed.

Conclusion : From the 68 tumours tested, five tumours had a MSI-h phenotype (7.35%), which is lower than cited in the literature.

THE IMPACT OF CAPSULE ENDOSCOPY ON THE OUTCOME OF PRESUMED BLEEDING OF SMALL INTESTINAL ORIGIN. M. Withofs, D. De Looze, G. Van Maele, M. De Vos. University Hospital Ghent, Belgium.

Aims. To evaluate the impact of the findings in capsule endoscopy (CE) and its relevance on the outcome of patients with digestive bleeding through long-term follow-up.

Methods. Capsule-endoscopy was performed consecutively in 25 patients referred for GI bleeding of unknown origin, after negative conventional work-up. If a relevant finding was found therapy was proposed to the referring physician. At follow-up all patient files were revised or the referring doctors were contacted in order to know the outcome of the patients.

Results. Twenty-five patients (7 females, 17 males, mean age 65 y, range 19-85) underwent CE for unexplained overt bleeding (hematochezia or melena) in 17 and iron deficiency anemia in 7. In 14 patients (56 %) a relevant finding was withheld : angiomas in 9 patients, ulcerations in 2, tumour in 1 and fresh blood only in 2. In 11 patients the CE was considered normal. The follow-up time ranged from 39-459 days (mean 199 d). One patient died 1 month after CE due to a cerebrovascular insult and was not included in the further analysis. In 9 of the 13 remaining patients no rebleeding was observed until now. Seven of them underwent specific therapy (coagulation of angiomas in 3, surgery in 3 and medical treatment in 1) and 2 patients had no therapy and didn't rebleed. The remaining 3 patients rebled, despite coagulation of angiomas in 3 and renewed, but negative, endoscopy in a suspected caecal bleeding on the CE. Of the 11 patients with a normal CE 7 didn't rebleed until time of follow-up, 3 rebled from another cause (1 hiatal hernia, 2 colonic angiomas) and 1 patient with von Willebrand's disease rebled of an unknown origin despite renewed work-up. Through these data we were able to calculate the following parameters for CE : sensitivity 100 %, specificity 69 %, PPV 69 % and NPV 100 %. There was no difference in outcome between patients with overt bleeding and occult bleeding.

Conclusion. Capsule-endoscopy has a definitive impact on patient outcome in more than half of the patients that present with GI bleeding of unknown origin after conventional work-up.

AMINOPYRINE BREATH TEST IN HOSPITALISED PATIENTS WITH HCV EN ALCOHOLIC CIRRHOSIS : COMPARISON WITH THE CHILD SCORE. D. Urbain (1), N. Petit (1), F. Mana (1), P. Van Hauthem (1), A. Bossuyt (2). (1) AZ VUB Dpt. of Gastroenterology Brussels, Belgium ; (2) AZ VUB Nuclear Medicine Brussels, Belgium.

The Aminopyrine Breath Test (ABT) evaluates the microsomal oxidative function of the liver. The test has a well known prognostic value in alcoholic cirrhosis. Few data exist concerning the place of the ABT in cirrhosis due to HCV infection. The aim of the present study was to evaluate the ABT in a cohort of hospitalised patients with decompensated HCV related- and alcoholic cirrhosis, and to correlate the results of the test with the Child score in both groups. Methods : between December 2002 and September 2003, all patients hospitalised for liver decompensation in the Gastroenterology Unit of the AZ VUB with proven cirrhosis of HCV etiology (n = 14) and alcoholic etiology (n = 71) were included in the study, after stopping medications susceptible to interfere with the result of the ABT. The Child score was calculated for each patient and an ABT was performed with ¹³C-aminopyrine. The proportion of ¹³C in breath samples was measured using Non Dispersive Infra-Red Spectrometry. Results of the test were expressed as the cumulated % of the administrated dosis excreted after 2 hours. Patients with simultaneous HCV infection and significant alcohol abuse were excluded of the study (n = 7). Linear regression and two-tailed Mann-Whitney tests were used for statistical analysis. Results : the proportion of patients classified as Child A, B and C respectively was not significantly different in the 2 groups of cirrhosis. The Child score was significantly lower in the group of HCV related cirrhosis : 7.5 + 2.1 versus 8.9 + 2.0 in the alcoholic cirrhosis group (P = 0.04). ABT values were significantly higher in the HCV group : 1.9% + 1.3, versus 1.3% + 2.0 in the alcoholic cirrhosis group (P < 0.02). Correlations between the results of ABT and the Child score were respectively r = -0.87 in the HCV group and r = - 0.52 in the group of alcoholic cirrhosis. Conclusions : hospitalized patients with decompensated cirrhosis due to HCV infection have a lower Child score and better results of the ABT than patients with alcoholic cirrhosis. Moreover, in the HCV patients group, the ABT results correlate better with the Child score. Although HCV infection is an important and frequent etiologic factor for liver cirrhosis, cirrhosis of alcoholic origin remains the most important etiology in patients hospitalized with a decompensated liver cirrhosis.

EFFICACY OF RABEPRASOL IN PATIENTS WITH BLEEDING PEPTIC DUODENAL ULCER. I. Kryvoruchko, V. Boyko, R. Smachylo, I. Sarian, V. Tarasenko. Institute of General and Urgent Surgery.

Objective : To evaluate the efficacy of rabeprazol ('Pariet') in patients with peptic duodenal ulcer complicated by bleeding.

Methods : 25 patients with peptic duodenal ulcer complicated by bleeding were analyzed. There were 18 males and 7 females. In 14 patients duodenal ulcer was revealed firstly. The remaining 11 patients suffered from peptic ulcer from 3 to 15 years, including 7 of them who had episodes of gastrointestinal bleeding in the past. All patients underwent laboratory tests, endoscopy by Fujinon EVE W-88A system, gastric pH-metry. Severity of gastrointestinal bleeding was assessed according to Shalimov A.A., 1970. All patients received rabeprazol ('Pariet') 40 mg two times per day during the first week and 20 mg per day during the next three weeks. Hemostatic treatment was conducted as well, blood transfusions were necessary in 8 patients. The efficacy of treatment was assessed clinically, by repeated gastric pH-metry and control endoscopy. Besides, any side effects of treatment were documented. Duration of follow-up was 6 months for 12 patients.

Results : The following clinical signs of the disease were observed on admission : fatigue (100%), melena (100%), bloody vomiting (24%), nausea (84%), heartburn (72%) and others. 16 patients had single ulcers, 9 patients had multiple ulcers. The mean size of ulcers was 0.96 ± 0.15 cm. Gastrointestinal bleeding of the I degree was in 8 patients (blood loss up to 20% of blood volume), II degree (20-30%) in 8 patients and III degree (more than 30%) in 5 patients. Gastric pH-metry on admission revealed hyperacidity in 21 patients (range 0.9-1.2), normal acidity in 4 patients (range 1.3-1.8). Complete healing of ulcers was achieved in 12 patients after two weeks, in 10 patients after three weeks and in 3 cases after 4 weeks. Rabeprazol treatment caused normal acidity in 10 patients, hypoacidity in 12 and anacidity in 3 cases. After 6 months hyperacidity was revealed in 3 patients, normoacidity in 9 among 12 patients that underwent pH-metry at this time. Side effects (diarrhea) were observed in 2 patients.

Conclusions : Rabeprazol is a highly effective treatment of peptic duodenal ulcer. Clinical improvement is observed during first 1-4 days of treatment and ulcer healing is achieved during 3 weeks.

AN ANIMAL MODEL OF COLON CANCER. M. El-Malt (1), P. Demetter (2), W. Ceelen (1), C. Cuvelier (2), M. Bracke (3), B. de Hemptinne (1), P. Pattyn (1). (1) Dept. of Surgery, UZ-Gent ; (2) Dep. of Pathology, UZ-Gent ; (3) Laboratory of Experimental Cancerology, UZ-Gent.

Objective : In spite of the use of rat colon cancer cell line CC531s in developing animal models of liver and lung metastases, it has been never used at its site of origin. In this study, we investigated the possibility of developing an animal model of colon cancer by using orthotopic implantation of CC531s cells in the colonic wall.

Methods : In 160 Wag rat, 5×10^5 CC531s cells were implanted in the subserosa in a predefined place of the sigmoid colon. The cells were either suspended in phosphate buffered saline (PBS) (group A, 80 rats) or in a mixture of PBS and Matrigel ; 50% each (group B, 80 rats). Each main group was divided into four subgroups (I, II, III & IV) including 20 animals each. One subgroup, from each main group, was sacrificed after 2, 3, 4 and 5 weeks. Macroscopically, the tumor diameter was measured in two dimensions. Hematoxylin-eosin (HE) staining and immunohistochemical staining (anti-tumor antibody CC25) were used to evaluate the tumor growth histologically.

Results : In group A, a 95% tumor growth rate was seen after 2 weeks and 100% starting from the third week onwards. In group B, the rate of tumor growth was 50%, 68%, 78% and 89% after 2, 3, 4 and 5 weeks respectively. The semiquantitatively scored number of tumor cells that was seen by HE staining did not differ significantly with time in group A. However, in group B, the number of tumor cells after 2 & 3 weeks was significantly lower than that was found after 4 & 5 weeks. By immunohistochemical staining, only the well-differentiated tumor cells could be identified. In both groups, the percentage of neoplastic cells stained with the anti-tumor antibody CC25 increased progressively with time.

Conclusion : Orthotopic implantation of CC531s cells in the colonic wall is a feasible and productive technique for developing an animal model of colon cancer. Matrigel has no positive influence on the rate of tumor growth.

EPITHELOID ANGIOSARCOMA OF THE RECTOSIGMOID. D. Creytens, A. Driessen, P. Pauwels. University Hospital Maastricht.

Primary angiosarcomas of the intestine are very rare tumors, resulting in diagnostic difficulties for the pathologists. The overall prognosis is very poor. Epithelioid angiosarcoma, as a subtype of angiosarcoma, can be hard to differentiate from poorly differentiated carcinoma without immunohistochemical stainings. Our case is a 73 years old male patient, whose initial complaints were slight (red) rectal blood loss. A colonoscopy showed two polyps, one in the rectum, another in the sigmoid, which were removed. First a diagnosis of a poorly differentiated carcinoma, infiltrating tubulovillous adenoma was made. Immunohistochemical studies showed endothelial differentiation of the tumor cells, fitting with angiosarcoma. Because of persistent blood loss, a low anterior resection was performed. The prognosis of this patient is poor as a CT scan of the lungs showed multiple metastases.

ACTIVATION OF HEPATIC STELLATE CELLS AND FIBROSIS IN HYPERVITAMINOSIS A : IMPORTANCE OF DAILY CONSUMPTION. MC. Nollevaux (1), Y. Guiot (2), Y. Horsmans (3), A. Geubel (3), J. Rahier (2), Ch. Sempoux (2). (1) Dept of Pathology, Clin Univ Mont-Godinne, Yvoir ; (2)Dept of Pathology, Clin Univ St-Luc, Brussels ; (3) Dept of Gastroenterology, Clin Univ St-Luc, Brussels, Belgium.

Hepatic stellate cells (HSC) store vitamin A in characteristic lipid droplets. In chronic liver injury, HSC undergo a myofibroblastic differentiation with alpha-smooth muscle actin (alpha-SMA) expression and high fibrogenetic capacity. In hypervitaminosis A, the spectrum of liver diseases includes non-cirrhotic portal hypertension, fibrosis or cirrhosis (1). We studied the relationship between HSC activation, fibrosis and vitamin A intake. In 9 patients with abnormal liver function tests, a liver biopsy was performed for the suspicion of vitamin A intoxication. The diagnosis was confirmed by histology and all other causes of liver injury were excluded by appropriate tests. A classical point-counting method (2) was used to quantify the volume density (Vv) of perisinusoidal and total fibrosis on sirius red stained sections and of sinusoidal and total activated HSC on sections immunolabelled for alpha-SMA (clone 1A4, Dako, 1/300). In one patient (daily dose : 50 UI 10³, total dose : 55000 UI 10³ ; 3 years of intake), liver architecture was preserved with numerous HSC rich in lipid droplets but few fibrosis and alpha-SMA labelling. In 5 patients (daily dose : 50-200 UI 10³, total dose : 55000-730000 UI 10³ ; 2.5-11 years of intake), marked perisinusoidal fibrosis and numerous alpha-SMA positive HSC were observed within the lobules. In the remaining 3 patients (daily dose : 150-400 UI 10³, total dose : 100000-300000 UI 10³ ; 3.5-4 years of intake), the liver showed severe lobular and portal fibrosis with a lot of alpha-SMA positive HSC in fibrous septa. In the whole series, Vv of total and perisinusoidal fibrosis ranged from 25.1 to 60.74% and 18.4 to 30.5% respectively and Vv of total and sinusoidal alpha-SMA positive HSC ranged from 2.1 to 21.6% and 0.12 to 11.0% respectively. There was a significant correlation between Vv of total fibrosis and Vv of total alpha-SMA positive HSC (p=0.016). A strong correlation between Vv of perisinusoidal fibrosis and the daily dose of vitamin A intake was also observed (p=0.004). In hypervitaminosis A, the development of fibrosis is thus correlated with the activation of HSC. The close correlation between the severity of perisinusoidal fibrosis and daily consumption of the vitamin strongly favours a dose-effect relationship.

(1) *Geubel et al. Gastroenterology 1991* ; (2) *Rahier et al. Diabetologia 1981*.

INVITED LECTURE

INDETERMINATE COLITIS. K. Geboes. Dept of Pathology, Univ Hospital Leuven.

A diagnosis of Crohn's disease and Ulcerative colitis is based upon a combination of clinical, histological, endoscopic and radiological data. The distinction between UC and CD can be difficult, due to the lack of a differentiating single gold standard. Indeterminate colitis was introduced by pathologists for the diagnosis of surgical colectomy specimens showing an overlap between the features of ulcerative colitis and Crohn's disease. The diagnosis of indeterminate colitis was based upon macroscopic and microscopic features. The term 'Indeterminate Colitis' is in recent years more widely applied to include all cases with endoscopic, radiographic and histological evidence of chronic inflammatory bowel disease confined to the colon, but without fulfilment of diagnostic criteria for ulcerative colitis and Crohn's disease. Like for ulcerative colitis and Crohn's disease, the diagnosis of indeterminate colitis has therefore become a clinicopathologic diagnosis. Indeterminate colitis is generally considered to be a temporary diagnosis. The clinical characteristics of patients with indeterminate colitis are however somewhat different from those with ulcerative colitis. Furthermore, serological markers such as pANCA and ASCA which are strongly linked with ulcerative colitis and Crohn's disease are both negative in a subset of patients with indeterminate colitis. Therefore, the possibility that indeterminate colitis could be a separate entity needs further investigation.

SQUAMOUS CELL CARCINOMA AND ANORECTAL FISTULAS IN CROHN'S DISEASE. C. Verbaandert (1), R. Detry (2), R. Fiasse (3), Ch. Sempoux (1). (1) Dept. of Pathology ; (2) Dept. of Surgery ; (3) Dept. of Gastroenterology, Clin Univ St Luc, 1200 Brussels, Belgium.

A 44 year-old female with a 22 year history of colic Crohn's disease, was hospitalized for severe loss of weight and asthenia. She complained of diarrhea and feces incontinence. Clinical examination revealed erythematous perianal skin with fistulous tracts and extensive anorectal induration. Biopsies taken during the rectosigmoidoscopy demonstrated the presence of a minimally invasive squamous cell carcinoma. Abdominoperineal excision was performed. Histological analysis revealed a peculiar feature of massive colonization of fistulous tracts by a keratinizing squamous cell carcinoma. It was notably extending into a fistula to the posterior vaginal cul-de-sac. None of the 38 lymph nodes examined were metastatic. After 6 months, a massive recurrence of the tumor was found in the pelvis and the patient died 9 weeks later. Patients with inflammatory bowel disease are at increased risk for developing cancer. Anorectal Crohn's disease, which often induces fistulas, leads to a chronic perianal inflammatory status that is believed to be a long-term predisposing factor of the development of anal carcinoma. Recent literature (1) suggests a poorer prognosis of this type of malignancy in a context of Crohn's disease, as illustrated by our case report. One explanation is that the diagnosis may be delayed because cancer symptoms are usually attributed to the inflammatory disease, also by the patient himself. Regular follow-up and adequate treatment of Crohn's perianal disease could result in better prognosis of this rare event.

(1) Ky et al. *Dis Colon Rectum* 1998 ; 41 :992-996.

SOLID PSEUDOPAPILLARY TUMOR : AN UNUSUAL PRESENTATION OF A RARE PANCREATIC TUMOR. N. Detrembleur (1), M. Demarche (2), Y. Denoel (2), E. Lismonde (2), J. Boniver (1), V. Fridman (2). (1) CHU Liège ; (2) CHR Liège.

Solid pseudopapillary tumor is rare and usually pointed out by an abdominal mass syndrome among female children and young adults. We report the case of a 16-year-old female admitted for haematemesis. First investigations showed oesophageal varices, cirrhosis and a 9cm through pancreatic tumor. Histological analysis showed a rare pancreatic tumor usually named solid pseudopapillary tumor. The characteristics of this tumor are discussed.

HISTOPATHOLOGICAL FINDINGS IN MUCOSAL BIOPSIES OF THE STOMACH OF PATIENTS RECEIVING ORAL IRON MEDICATION. R. Croes, N. Ectors, K. Geboes. Dept of Pathology, Univ. Hospital, Leuven.

Introduction : Oral iron supplements are widely administered in the community. Severe, sometimes lethal damage to the upper gastrointestinal tract following overdose is well known, but there is less appreciation of the mucosal injury and the clinicopathologic spectrum that can be caused by therapeutic iron dosage.

Materials and methods : Six patients (2 male, 4 female, mean age of 64.8 y) underwent endoscopy of the upper gastrointestinal tract for abdominal pain (n=2), anorexia after liver transplantation (n=1), weight loss (n=1), follow-up of ulcer disease (n=1) and follow-up of oesophageal varices (n=1).

Results : The gastric endoscopy was normal in three patients. In the other three patients a gastric ulcer was present. Mucosal biopsies were submitted for routine histology. Reactive gastritis was present in four patients, *Helicobacter pylori* negative active chronic gastritis in two patients, and erosive/ulcerative mucosal injury in three patients. Closer evaluation of the biopsies revealed a conspicuous brownish pigmentation of the basal cytoplasm of the oxyntic (parietal) cells frequently located at the base of the glands, a faint but evenly pigmentation of the mucous neck cells, a strong pigmentation of interstitial macrophages in the upper lamina propria and of the mucin in foveolar crypts. The intensity of pigmentation was more pronounced in cases with mucosal injury than in cases without mucosal injury. No pigmentation was found in the surface-foveolar mucous cells or in the zymogenic (chief) cells. The presence of crystalline iron deposition was proven by a Perl's stain in all biopsies. Oral iron medication was confirmed in all patients and no other aetiology of gastric melanosis apart from oral iron supplements could be identified. A duodenal tubular adenoma with light dysplasia was found in one female (59 y).

Conclusion : These results prove that iron in therapeutic dosage can induce pigmentation with injury to the gastric mucosa or may exacerbate erosive mucosal injury especially in patients with already associated upper gastrointestinal disorders. The identification of iron pigment in the tissue is a marker of this condition. Histopathological recognition and reporting of iron-induced changes in endoscopic biopsies by pathologists to clinicians may aid in optimizing diagnosis and therapy of gastric discomfort. However, the pathologist should be conscious of other causes of brownish pigmentation of the gastric mucosa. A Perl's stain should therefore be performed to confirm the diagnosis of iron gastritis.

HUMAN INTESTINAL SPIROCHETOSIS : A REPORT OF 24 CASES. W. Develter, N. Ectors, K. Geboes. Dept of Pathology, Univ Hospital Leuven.

Introduction : Human intestinal spirochetosis (HIS), characterized by end-on attachment of densely packed spirochetes to the epithelial surface of the large intestine has been associated with the presence of weakly beta-hemolytic spirochetes *Brachyspira aalborgi* and *Brachyspira (Serpulina) pilosicoli*. It has been documented that some spirochetes are involved in enteropathies in animals. The pathogenic potential and clinical significance of human intestinal spirochetosis is still controversial.

Materials and methods : We reviewed the clinical data and histology from a series of 24 patients with HIS diagnosed at the KUL over the past 25 years. We compared sex, age, symptomatic and asymptomatic patients and macroscopic vs. microscopic anomalies.

Results : HIS was twice as frequent in men as in women (62,5% in male, 37,5% in women) and was most common in the fifth decade. Only 3/24 patients were asymptomatic. Abdominal pain and diarrhea were present in more than 50% of the cases (abdominal pain 32%, diarrhea 21%). Endoscopy was normal in 2 of the 3 asymptomatic patients whereas only 8 of 21 patients of the symptomatic group had no macroscopic anomalies. All asymptomatic patients and 81% (17 of 21 patients) of the symptomatic patients showed no microscopic abnormalities except for the presence of the classic dark blue brush border on the surface epithelial cells, characteristic for the condition. Only in three cases an inflammatory cell reaction was seen in the lamina propria. In two of these cryptitis was also present.

Conclusion : HIS is characterized by the microscopic appearance of a bluish brush border covering the luminal surface of epithelial cells in the colon. HIS seems more frequent in adults. It occurs however also in children. No specific symptom-complex is associated with HIS, although many patients have complaints. Histopathological recognition and reporting of HIS to clinicians may thus help in explaining abdominal complaints *e causa ignota* of a patient. Treatment with Neomycine and/or metronidazole should be considered especially in immunocompromised and in homosexual patients as in this population symptomatic HIS is most frequent.

PROGNOSTIC VALUE OF FAS EXPRESSION IN PANCREATIC ADENOCARCINOMA. P. Demetter (1), S. Claeys (2), M. Peeters (3), B. de Hemptinne (4), C. Cuvelier (5). (1) Pathology, Ghent University Hospital ; (2) Pathology, Ghent University Hospital ; (3) Gastroenterology, Ghent University Hospital ; (4) Surgery, Ghent University Hospital ; (5) Pathology, Ghent University Hospital

Background : Based on the histopathological assessment of pancreatic cancer resection specimens, prognostically relevant factors are known. However, the knowledge of additional factors associated with the prognosis might be helpful in planning the therapy for an individual patient.

Methods : We investigated paraffin-embedded specimens of 25 patients undergoing surgical treatment for adenocarcinoma by immunohistochemistry to assess the expression and the prognostic impact of p53, Ki-67, Bcl-2, Fas and MMP-9. The number of positive neoplastic cells and the intensity of staining were scored semiquantitatively. The presence of micrometastases in locoregional lymph nodes was studied by staining for low molecular weight-cytokeratins. Neither survival time nor disease-free survival time were known at the time of the investigation.

Results : No correlation was established between immunohistochemically detected micrometastases and prognosis. The expression of p53, Ki-67, Bcl-2 and MMP-9 did not influence the survival or disease-free survival. Expression of Fas, however, was associated with longer disease-free survival (P=0.014).

Conclusion : Fas exerts an influence on prognosis in adenocarcinoma of the pancreas. However, further investigations in larger patient samples are required to confirm these results.

INVITED LECTURE

EARLY DYSPLASIA IN IBD. R. Riddell, Lab Medicine and Pathobiology, University of Toronto, Mount Sinai Hospital, Toronto, Ontario, Canada.

Early dysplasia : There is no definition of “early dysplasia”. Epithelium is either not dysplastic, unequivocally dysplastic or indefinite for dysplasia. Dysplasia can be subdivided into high grade (HGD) and low grade (LGD). There is no literature on therapy for mild, moderate or severe dysplasia, so these terms should be actively avoided. While “severe” dysplasia may be the equivalent of HGD, it is unclear what moderate or low grade dysplasia parallel. Mild could even mean indefinite. No treatment options can be based on this. Early dysplasia can therefore be considered a) chronologically in the evolution of dysplasia in a patient e.g. the first time it is found in a patient who has undergone regular surveillance colonoscopies, OR b) it may be considered in molecular terms of which there are many but which include the finding of p53 mutations (or immunoreactivity), aneuploidy, abnormalities in mismatch repair genes or their proteins in patients with biopsies that are not overtly (unequivocally) dysplastic. The problem with these changes is that there are no few data on their natural history, although it intuitively puts the patient in a higher risk category for dysplasia/carcinoma when compared to patients without these abnormalities. Handling patients with HGD is relatively non-controversial, because most patients come to colectomy unless an adenoma/adenoma-like mass is present that can demonstrably be completely removed locally, AND no further dysplasia is present elsewhere. LGD except in an adenoma/adenoma-like lesion remains controversial and to some extent philosophical/emotional and may depend on the degree of cancer phobia of the physician or patient. There are the hawks and the doves. The hawks have often been bitten by unsuspected and lethal carcinomas in young patients (the mean age of colitic cancers remains in the 40-45 age range, so by definition ? are younger than this), and have no desire to repeat the trauma involved. A major problem in following LGD is a) what is the next endpoint for therapy – “persistence/confirmation” of LGD (?= not completely removed previously), but if not found again this may represent sampling, multifocality (of what), the development of HGD or finding of incidental carcinoma colonoscopically with the hope that it is curable. Changes “indefinite for dysplasia (IFD)” are not only very subjective (definitions vary depending on whether one accepts maturation as being always part of repair, and therefore indefinite by definition, or whether dysplasia can mature (I am in the latter camp) BUT their implication open to question. However, increasingly, if overtly regenerative changes are not present, then IFD seems to be “the low end of LGD” and tends to behave similarly to LGD with regard to the likelihood of dysplasia or carcinoma either being present elsewhere in the bowel or developing subsequently. This seems to hold for both Barrett’s Esophagus and UC. More data are required especially regarding the risk of a) current b) subsequent invasive carcinoma and it.

NUTRITION SUPPORT TEAMS IN BELGIUM. J.C. Preiser (1), A. Bailly (2), A. Van Gossum(3) from (1) University Hospital of Liege, (2) CHU Charleroi and (3) Erasme University Hospital, Brussels.

In Belgium, there is presently no legal constraint for an hospital to organize a nutritional support team, and there is no national registry of these teams. In addition, the French- and Dutch-speaking societies of clinical nutrition are not informed of the current status of nutrition support teams. In order to address the following questions : (1) how many hospitals do have a nutrition team, (2) what is the composition of these groups and (3) what are the activities of these groups, we performed a survey on behalf of the societies of nutrition, via a questionnaire sent to the medical directors of the Belgian hospitals. There were nutrition support groups in 24 of the hospitals (22%). The frequency of the meetings of these groups ranges from between once a week to once a year. The nutrition support groups include physicians (88 %), dietitians (96 %), pharmacists (75 %) and nurses (71 %). The activities of these groups include the selection of products for enteral feeding (92 %), dietary complements (92 %), solutions for parenteral nutrition (75 %), the presentation of scientific talks (50 %), presentation of products by companies (42 %) and performance of scientific work (45 %). Proceedings of individual meetings and annual reports of activity are performed by 63 and 21 % of nutrition support teams, respectively.

SCREENING FOR MALNUTRITION IN HOSPITALIZED PATIENTS : A CLINICAL DETECTION TOOL. L. Van Looy, H. Van der Mussele, AZ Sint-Augustinus, Antwerpen.

Objectives : to improve the awareness of the caregivers concerning the occurrence of malnutrition in their own patient-population, by documenting the problem. To define a clinical pathway for early detection of malnutrition in adult patients admitted to a general hospital, with maximal use of modern information technology available in the hospital information system (HIS) for automatic processing of the procedure, and to implement measures for improving the nutritional status of these patients.

Method : first a registration of the BMI of all patients 16 years or older admitted to the hospital during a 1 month survey period was performed to have a raw idea of the magnitude of the occurrence of malnutrition. Then a clinical pathway (CP) was developed, where BMI and loss of body weight in the past 3 months were chosen as critical indicators. Maximal use of information technology at hand and minimal use of human resources were looked for. The critical indicators are registered on admission and weekly during hospital stay. Automatic messaging by the HIS to the dietary department of the patients of risk generates a subjective global assessment (SGA) by a dietician and, if appropriate, a dietary or medical advice. Nutritional therapy is then started after consent of the patient and his treating physician. Follow-up of the evolution of the nutritional status on a twice weekly basis is performed and triggers sequential visits of the dietician or discharge from the CP once the critical indicators are no longer trespassed. Messaging to the treating physician is accounted for by means of computerised notes in the patient file. If the patient does not reach the stated goals on discharge from the hospital, a proposal is made for nutritional follow-up by the general practitioner or on an outpatient-basis in the dietary service of the hospital. The CP has been running on trial for 7 months in 3 hospital wards now. Refinement by registration of the daily food intake and objectifying nutritional improvement is planned. Finally the CP will be implemented for all adult patients on all general wards. The continuing shortening of the hospital stay and the growth of treatment on an outpatient-basis form the major obstacles for the described type of intervention. This makes the sensitisation and involvement of first-line caregivers mandatory.

IS IT POSSIBLE TO IMPLEMENT A SCREENING TOOL FOR DETECTING MALNUTRITION IN HOSPITALIZED PATIENTS ? S. Vereecken, A. Van Gossum. Brussels, ULB.

Malnutrition is frequent in hospitalized patients. A survey that has been performed in the Unit of Gastroenterology at Erasme Hospital in 2002 has shown a prevalence of 40% of malnourished patients in a cohort of 160 patients (1). Amongst them, 20% of patients presented signs of severe malnutrition. A rapid screening tool was validated and likely to detect 80% of severely malnourished patients (2). This screening tool includes : percentage of weight loss >10% and 2 questions : did you loose weight ? Did you loose appetite ? If the 3 items were positive, the patient was highly suspected to be malnourished. The next step was to implement this screening tool at the time of admission of the patients. During a period of 3 months (from November 2003 to January 2004), each patient received at admission a questionnaire that was collected by the dietician working at the floor. Results of this strategic approach will be given and discussed.

Montois C et al, Clin Nutr 2003 ; 22, suppl 1.

Drumel et al, Clin Nutr 2003 ; 22, suppl 1.

HYPERGLYCEMIA IN PARENTERAL NUTRITION : PREVALENCE, RISK FACTORS AND EFFICACY OF INSULIN ADDITION TO THE BAGS. A. Ceratti, J. Verniers, J.M. Ketelslegers, J.P. Thissen. Diabetes and Nutrition Unit, University of Louvain, Belgium.

Hyperglycemia is one of the most common metabolic complications in parenteral nutrition (PN). Our goal was to assess the prevalence and the risk factors for hyperglycemia in PN-fed patients and to investigate the efficacy of insulin addition to PN's bags on glycemia. The study was performed at the St-Luc Academic Hospital (Brussels) with 158 consecutive PN-fed patients previously not insulin treated. Among them, 63% were fed a binary PN (80% with lipids in parallel) while 37% were fed a ternary PN. The mean caloric intake was 26.3 ± 0.6 kcal/kg/j with 2.97 mg glucose/kg/min and 1.3 g amino acids/kg/j. Capillary glycemia was measured every 6 hours during the first 48h of PN. Hyperglycemia, defined as mean nycthemeral glycemia over 180 mg/dL or first glycemia over 270 mg/dL, was observed in 26% of PN-fed patients during the first 24h. Age over 60, use of hyperglycemic medications (glucocorticoids, somatostatin, cyclosporin, and tacrolimus) and pancreatic-biliary surgery were associated with a higher risk of hyperglycemia. Risk of hyperglycemia was independent of the rate of glucose infusion. In patients where mean nycthemeral glycemia during the first 24h was over 180 mg/dL (n=29), insulin addition to the bag (1 UI for 10 g glucose) during the second day decreased glycemia by 26% (from 215 to 159 mg/dL ; $p < 0.001$), without any hypoglycemia. Measurements of insulin concentrations in the bag showed that adsorption is relatively large for binary mixtures (30-50%), but almost inexistent in ternary mixtures. Insulin adsorption to the bag was stable with time, without any delayed release of insulin. Moreover, adsorption to the administration set was non significant. Finally, addition of sodium bicarbonate (a general use in our Institution) did not decrease insulin adsorption.

Conclusion : Insulin addition to the bag is efficient to control hyperglycemia in PN-fed patients. This technique should therefore be more frequently used, as clinical evidence indicates that strict control of glycemia improves the prognosis of critical ill patients in hospital.

CHANGES IN PLASMA LIPOPROTEIN CONCENTRATION AND COMPOSITION FOLLOWING CARDIAC SURGERY. M. Hacquebard*, A. Ducart**, D. Schmartz**, N. Tembo*, Y. A. Carpentier*. *L. Deloyers Laboratory for Experimental Surgery, **Dpt of Anaesthesia, Erasme hospital ; Université libre de Bruxelles, Brussels, Belgium.

Rationale : The acute phase response (APR) is a systemic reaction to infectious and non-infectious injury in which multiple metabolic adaptations are induced by hormonal changes and inflammatory cytokines. This host response includes changes in the hepatic synthesis of several plasma proteins but also profound alterations in plasma lipids and lipoproteins. The aim of this study was to determine changes in concentration and composition of plasma LDL and HDL after cardiac surgery.

Methods : The study group included 15 patients undergoing coronary artery bypass grafts or valve replacements. Patients with hepatic or renal failure and/or diabetes were excluded. Blood samples were withdrawn at the time of anaesthesia induction and again at day 2 post-surgery. LDL and HDL were isolated by sequential ultracentrifugation. Apolipoproteins (apo B, AI, SAA), lipids [total cholesterol (TC), free cholesterol (FC), phospholipids (PL), triglycerides (TG)], vitamin E and peroxides were analysed in each sample. Statistical analyses were made with the paired Student's t test. Results : Cardiac surgery was associated with a marked decrease in LDL-TC (-41% ; $p < 0.001$) and LDL-Apo B (-44 % ; $p < 0.0001$) reflecting a reduction in the number of circulating particles. In HDL an abrupt rise of SAA (>1000 fold ; $p = 0.04$) was observed together with a decrease in Apo AI (-24% ; $p = 0.002$). Vitamin E was reduced by 40 % ($p < 0.0001$) and 25 % ($p < 0.001$) in LDL and HDL fractions, respectively. This was largely due to the decrease of circulating LDL and HDL particles. The content of FC and PL was increased ($p < 0.05$) in both particles. The peroxide content was increased in LDL ($p = 0.017$) and HDL ($p = 0.08$).

Conclusions : The acute phase response post-cardiac surgery induces a marked decrease in the number of circulating LDL particles suggesting a margination out of the vascular compartment. Changes in HDL composition are consistent with decreased protective properties.

TECHNIQUES OF PARENTERAL NUTRITION IN SMALL ANIMALS. M. El-Malt (1), P. Pattyn (2). (1) Department of Surgery, Ghent University Hospital ; (2) Department of Surgery, Ghent University Hospital.

Preclinical studies are important steps in new drug investigation and therapy evaluation. The use of small animals (rat and mice) is cost effective regarding the prices of animals and materials and the required space to keep the animals. The availability of suitable techniques and materials allows performing of different studies using parenteral nutrition in small animals. Two techniques are available to apply parenteral nutrition in rats and mice. In the tail-cuff technique, the IV catheter is forwarded through the femoral vein to be situated inside the IVC, the other end of the catheter is exteriorized through the animal tail. In the shoulder-jacket technique, the catheter is inserted through the jugular vein so that the tip is situated inside the SVC while the other end is exteriorized through the back of the neck. With the use of an infusion set, both techniques would facilitate continuous IV infusion and allow free mobility of the animal while it is connected to the infusion pump. The catheters used in both techniques are either made of silicon or polyurethane, mostly with rounded tip to minimize the initial irritation and an adjustable suture bulb to insure proper fixation of the catheter. A heparin-coated version of the polyurethane catheter is available and could be used to minimize the fibrin deposition and thrombogenic effects. Parenteral nutrition in small animals using the above mentioned techniques is technically feasible and allows a wide range of experimental studies. In our own experience, we could keep the rats on total parenteral nutrition for three weeks using both techniques without significant morbidity or mortality. {{P.S. The presentation of this abstract would include the practical details regarding both techniques with a short video (2 minutes) showing the tail-cuff technique}}

SOMATOSTATIN ADDED TO A TPN-MIXTURES IN THE TREATMENT OF FISTULA. G. Roeyen (1), T. Chappelle (1), H. De Bosscher (2), E. Mattheussen (2), M. Ruppert (3), D. Ysebaert (1). University Hospital Antwerp : (1) Dep. of Hepatobiliary, endocrine and transplantationsurgery ; (2) Nutrition team ; (3) Dep. of Abdominal Surgery.

Study objective : Somatostatin and total parenteral nutrition (TPN) are routinely used in the treatment of pancreatic and enterocutaneous fistula. This study was performed to determine whether somatostatin should be administered by a separate intravenous line, or could be added safely to the TPN-mixture. When somatostatin is added to a TPN-mixture, only one intravenous line is needed for administration of both drugs, leading to less manipulation by the nursing staff and therefore less administration errors.

Methods : 8 patients with a pancreatic or a enterocutaneous fistula were treated with a standard TPN-mixture (Kabiven 14 - Fresenius) and somatostatin (Somatostatin-UCB ®) 6 mg/day. When somatostatin was added to the TPN-mixture, samples drawn immediately after preparation, 4 and 24 hours after preparation were analysed to determine somatostatin availability. Patients were randomized to two possible treatment regimens : 'TPN with somatostatin added - TPN and somatostatin separately - TPN with somatostatin added' or 'TPN and somatostatin separately - TPN with somatostatin added - TPN and somatostatin separately'. Each regimen consists of 9 days of therapy and was continued in a separate setting when clinically necessary. During treatment, serum levels of somatostatin were measured daily and pre- and post-treatment samples were also analysed.

Results : Samples drawn from the mixture, immediately, 4 hours and 24 hours after preparation demonstrated a somatostatin availability of more than 100.000 pg/ml. Normal values of endogenous somatostatin rank below 110 pg/ml. When somatostatin was infused through a separate intravenous line, the mean patient's serum level of somatostatin was 932 pg/ml (SD = 546). When somatostatin is added to the TPN and infused 'all in one', mean serum level of somatostatin was 905 pg/ml (SD = 477). The mean pre- and post-treatment serum level was 19 pg/ml (SD = 7).

Conclusion : When added to a TPN mixture somatostatin is still fully available in the TPN-mixture 24 hours after preparation. The mean serum level of somatostatin is comparable in both treatment regimens. Therefore somatostatin can be added safely to a TPN-mixture.

HOME PARENTERAL NUTRITION IN CANCER PATIENTS : ON WHICH CRITERIA TO START IT? A. Van Gossun, A. Ballarin, V. Liévin. Brussels, ULB.

Home parenteral nutrition (HPN) has been initially designed for patients who were suffering of intestinal failure related to benign diseases. However, since 10 years, carcinomatosis with chronic occlusion appeared to be one of the major indications for HPN in US but also in Europe (1).

Some surveys have shown that the mean survival time for these cancer patients is about 4 months. A few studies have evaluated their quality of life. Some criteria have been proposed in order to better select cancer patients who could benefit of HPN. A Karnofsky score superior to 50 is one of the most valuable criteria. Here, we critically reviewed our experience in Erasme Hospital of providing HPN in cancer patients. Inclusion criteria will be critically discussed.

VAN GOSSUM A et al, Clin Nutr 2002.

BOZZETTI F et al, Clin Nutr 2003.

VIDEOFLUOROSCOPIC ASSESSMENT OF SWALLOWING IN INFANTS AND CHILDREN. A. De Vriendt (1), C. Hoskens (2), G. Veereman-Wauters (1), T. Mahler (1), M. Van Caillie-Bertrand (1). (1) Pediatric Gastroenterology and Nutrition AZ Middelheim ; (2) Pediatric Radiology AZ Middelheim.

Efficient swallowing transports nutrients and secretions from the mouth to the esophagus, without substances entering the airway. The clinical examination provides information about the oral mechanisms, but a radiological study is necessary when a child is suspected of oropharyngeal swallowing problems. Videofluoroscopic assessment is always preceded by a clinical examination by a gastroenterologist and a clinical evaluation of the oral mechanisms with a feeding observation by a speech pathologist. Videofluoroscopy is performed by a radiologist in cooperation with a speech pathologist. The anatomy of the oral cavity, the pharynx and the cervical esophagus is visualized and their functionality dynamically assessed. The radiologist is specifically trained to see anatomical defects while the speech pathologist has more knowledge of the oropharyngeal movement patterns during swallowing and the therapeutic recommendations for treatment of the multiple disorders. Disorders in movement patterns that control the bolus and cause aspiration or inefficient swallowing can be detected. In the oral phase problems can be observed in tongue movements, tongue-palate contact, collection and propulsion of the bolus, oral transit time and clearance of the mouth. In the pharyngeal phase premature spilling in the valleculae and the piriform sinuses can be observed, as well as the trigger of the pharyngeal swallow, velopharyngeal closure, movement of the hyoid bone, elevation and closure of the larynx, downward movement of the epiglottis, laryngeal penetration or aspiration and the time when it happens, contractility of the hypopharynx, residue in the valleculae, the piriform sinuses or the posterior pharyngeal wall, pharyngeal transit time and the number of swallows to clear the bolus. In the early esophageal phase problems with the opening of the upper esophageal sphincter can be observed. Videofluoroscopic assessment needs to be integrated with findings from clinical and instrumental examinations. Thus, treatment strategies to eliminate aspiration and increase swallowing efficiency can be designed. This will be illustrated with case reports.

INTERVENTIONAL ABDOMINAL RADIOLOGY. Ph. Clapuyt, Ch. Saint Martin, R. Menten, D. Claus Brussels,UCL.

In our experience, the most frequent abdominal procedures performed in children are listed below :

- Biopsies or punctions : liver, kidney, tumours, ...
- Drainages : abscesses, nephrostomy, bladder derivation ...
- Balloon dilatation of strictures : oesophagus, bile ducts,...
- Pneumatic reduction of ileo-caecal intussusception
- Pancreatic selective venous sampling

The specificity of interventional radiology in children is the small size of the patient and the need for specific material or usually adaptation of adult material.

The preparation of the procedure is of great concern : availability of previous radiological examinations and real time visualization of the anomalies with ultrasound is mandatory.

Sedation or anaesthesia is always required. In our institution we collaborate with the team of paediatric anaesthetists.

Guidance is mostly performed by ultrasound but fluoroscopy and seldom CT scan can also be used.

Some examples of technical procedures and the results of our short series of selective pancreatic venous sampling for infantile hyperinsulinism will be presented during the plenary session.

Reference : Katz ME, Kolm P, Intussusception reduction 1991 : an international survey of paediatric radiologists. *Pediatr Radiol* 1992 ; 22(5) : 318-22

WIRELESS VIDEO-ENDOSCOPY OF THE SMALL BOWEL IN CHILDREN. B. Hauser, K. De Vogelaere, D. Urbain, Y. Vandenplas. AZ-VUB, Brussels, Belgium.

Wireless video-endoscopy of the small bowel is a relatively new diagnostic tool for which there is limited paediatric experience. In a 5 year old child, known with a vascular anomaly of the airways that had been embolised, the video-endoscopy was performed because of anaemia of unknown origin. To exclude a gastrointestinal cause for her anaemia, initially an oesophagogastroduodenoscopy and ileocolonoscopy were performed and were normal. A video-endoscopy was performed to exclude a vascular malformation of the small bowel and was also normal. A second child of 8 years, with uneventful history, presented with recurrent episodes of acute abdominal pain with vomiting and diarrhoea. Different ultrasonographies showed a recurrent ileo-ileal intussusception and mesenteric adenitis. Other investigations including biology, stool cultures, scintigraphy and transit were normal. As there was no clear explanation for these episodes of recurrent ileo-ileal intussusceptions, a video-endoscopy was performed. Although the invagination was recorded by the capsule, no underlying cause could be demonstrated.

CLINICAL SPECTRUM OF ACHALASIA IN CHILDHOOD. W. De Rouck (1), I. Hoffman (2), V. Janssens (2), M. Van Winckel (3), PH. Alliet (1). (1) Virga Jesseziekenhuis, Hasselt ; (2) UZ Gasthuisberg, Leuven ; (3)UZ Gent

Objectives : To describe the spectrum of presenting symptoms, initial diagnosis and delay to final diagnosis in children with achalasia.

Methods : Retrospective study of children with final diagnosis of achalasia in three Flemish hospitals during a period of 10 years.

Results : In 8 patients (5 male, 3 female ; mean age : 7,82 y (3,8 - 15,5 y) finally diagnosed as having achalasia, 4 were initially diagnosed with asthma or recurrent lower airway infections (N : 3), or with anorexia nervosa (N : 1). Mean delay to diagnosis of achalasia was 9 months (1-36 mths). Presenting symptoms were weight loss (N : 4 ; mean : - 1,08 kg), dysphagia for non-liquid foods (N : 5, in all increasing with time) ; dysphagia for liquids (N : 1) , odynophagia (N : 5), nightly regurgitation (N : 5), vomiting (N : 7, saliva, non-digested foods) ; recurrent coughing (N : 3). In all patients, the diagnosis of achalasia was suggested on barium swallow and confirmed by oesophageal manometry. Seven patients were treated with a Heller myotomy and anti-reflux surgery (1 patient underwent multiple dilatations before final surgery).

Discussion : The diagnosis of achalasia in children is often delayed. The presenting symptoms can be very subtle and misleading. A thorough history with emphasis on night-time vomiting of liquids and solids, odynophagia, dysphagia for solids and recurrent coughing is important. Regurgitation during sleep or in horizontal position is a frequent complaint. Achalasia should also be considered in patients with chronic pulmonary infections or anorexia nervosa, especially when not responding to conventional treatment or worsening of the symptoms with time.

LOCALISATION OF LANGERHANS CELL HISTIOCYTOSIS IN THE GASTRO-INTESTINAL TRACT WITH THE ONCO- PET SCAN : A CASE REPORT. A. Huybrechts (1), T. Jonckheer (2), P. Maes (3), H. Slabbinckx (4), T. Mahler (5), G. Veereman (6), M. VanCaillie-Bertrand (7), J. Van De Vivere (8). (1) Pediatric Gastroenterology, AZ Middelheim ; (2) Pediatric Pneumology, AZ Middelheim ; (3) Pediatric Hematology, AZ Middelheim ; (4) Pneumology, AZ Middelheim ; (5) Pediatric Gastroenterology, AZ Middelheim ; (6) Pediatric Gastroenterology, AZ Middelheim ; (7) Pediatric Gastroenterology, AZ Middelheim ; (8) Isotopes, AZ Middelheim.

A 14 year old boy was admitted with cough, hemoptoe, night sweats, anorexia without weight loss and bouts of epigastric pain since 4 weeks. Physical examination showed a not acutely sick boy, slightly pale, with no temperature, no hepatosplenomegaly, no adenopathy. Height : 156 cm (P25) Weight : 51.5 kg (P50). Rhonchi on right lung. Mantoux : Negative. Laboratory examination : increased inflammatory parameters (CRP : 2.3 mg/dl ; sedimentation rate : 58 mm/h) with mild anemia. Chest X-Ray and CT-Scan showed 2 important masses in the right lung. Bronchoscopy showed an endobronchial mass. Biopsies were taken. Histology revealed the diagnosis : Langerhans Cell Histiocytosis. The Onco-Pet Scan was performed to search other localisations. It showed the primary tumor in the right lung, but also a very extensive and unexpected localisation in the stomach and duodenum. This was further confirmed by endoscopy and biopsy.

SCINTIGRAPHY WITH TC99M-LABELED LEUCOCYTES AS DIAGNOSTIC AND FOLLOW UP OF IBD IN CHILDHOOD. A. Sengier (1), M. Scaillon (1), P. Bontems (1), P. Martin (2), S. Cadranel (1). (1) Gastroenterology, HUDERF ; (2) Nuclear Medicine, Brugmann Hospital.

Tc99m-labeled leucocytes are concentrated in inflammatory zones and scintigraphy can reveal the suspected lesions in IBD. **Aim** : stress the interest of scintigraphy as a diagnostic and follow up tool in children presenting with IBD in comparison to endoscopy and histology.

Methods : Scintigraphy was performed using autologous leucocytes labeled with Tc99m following either the 'in vivo' technique of monoclonal antibodies injected directly either the 'in vitro' extemporaneous labeling technique of monoclonal murine antibodies coupled with hexamethyl-propyleneamine oxime (HMPAO). Total colonoscopies with multiple biopsies were performed contemporaneously in 25 children (9F/16M) suspected of IBD. The hyperactive scintigraphic sites were compared to the endoscopic lesions and histologic findings. Two or more follow up scintigraphic studies are available in 20 children.

Results : Scintigraphic results showed inflammatory sites in 24/25 cases. A good correlation with the colonoscopic lesions and pathologic findings was found concerning the intensity and the site of inflammation. The final diagnosis was Crohn's disease in 16 cases, UC in 6 and indeterminate colitis in 3. The scintigraphic method is reliable but non-specific and detects any inflammation such as a Yersinia enterocolytica-related colitis or Blastocystis hominis colonic infection or the rare interstitial pulmonary disease complicating the Mesalazine treatment of a child with UC.

Conclusions : Tc99m-labeled leucocytes scintigraphy is a non invasive but non specific method of detection of the intensity and extension of inflammatory processes in IBD. There is a good correlation with endoscopy. Better results are obtained with the 'in vitro' Tc99m-HMPAO labeling of the leucocytes which becomes a useful method for the follow up of IBD in children.

HIGH RESOLUTION ULTRASONOGRAPHY IN EARLY CLINICAL STAGE OF CHRONIC INFLAMMATORY BOWEL DISEASES (CIBD). J Khamis, A Nchimi, E Ponte, R Ouhadi, I Paquot, F Bury. CHC- Liège, Clinique de l'Espérance, 447 rue Saint Nicolas 4420 Saint Nicolas Liege.

Introduction : The goal is to evaluate the possibility of high resolution ultrasonography, to detect precociously parietal modifications related to a pathological process such as CIBD for better guiding endoscopic biopsy (E B) and to allow an adequate and early treatment.

Material and methods : We reviewed the clinical and US files of the 10 newly cases of CIBD diagnosed in our institution between October 2000 and March 2003 (29months). All the children underwent an US and E B (n=10).

Result : Clinical signs were abdominal pain (n=6),diarrhea (n=9) , bloody diarrhea (n=4), lasting since less than 2 weeks (n=4), for 2 months (n = 3) with weight loss (n=5).There was an average of 3,7 days between clinical exam and US. In only one case the US was performed after the EB. In all the other cases (n=9) CIBD diagnosis was not established before the US. US shows typical signs of Crohn's disease (CD) with moderate dedifferentiated, wall layers thickening (n=2), and a perigit sclerolipomatosis (n=1). Separately, US CIBD signs are not specific but associated to the clinic features, was suggestive for CIBD (n=7). In one case CIBD was not suggested because of acute clinical course. The final diagnosis was : CD (n=7) and RCUH (n=3).

Discussion : The good specificity of high resolution US is well known in the follow-up of the advanced CD where it shows thickening and inflammation of the five layers wall and perigit sclerolipomatosis. The mucosal and sub-mucosal ultrasonographic thickening observed in early stage is not specific. Indeed they are common to the CD, the RCUH and infectious ileocolitis as salmonellas, shigellosis, or campylobacters. Yersiniosis infection would have a different US signs. We found anomalies of the intestinal wall, mainly hyperaemic thickening in the sub mucosa in all the cases (n=10) attesting a great sensitivity of the technique. Two of the children presented an advanced CD had a typical US signs while at the others (n=8) the disease was still at early stages. In these cases in spite of lesser US specificity, the knowledge of the clinical history of children had allowed to suggest (n=7), or to confirm IBD (n=2) and to perform an EB within average 6, 8 days afterwards. In one case, because the acute clinical presentation (diarrhea of less than 24 hours), the US anomalies observed were wrongfully allotted to an infectious origin that clinical evolution cancelled.

Conclusion : High resolution sonography, safe, non-invasive easy to access, well accepted by the patients, is a very sensitive method to characterise the child intestinal wall as in CIBD and to guide precociously the (E B). It became a usual help of clinical exam each time a gastrointestinal pathology is suspected.

GUIDELINES IN IMAGING OF PAEDIATRIC GASTROENTEROLOGY. LG. Rausin, P. Jamblin, H. Bostem. CHR Citadelle.

With the explosion of new technologies, the medical imaging department has to manage an increasing demand for different examinations. Paediatric radiologists have to face three main challenges :

1. Increase diagnostic efficiency.
2. Look after delivering an irradiation 'As Low As Reasonably Achievable' (ALARA principle)
3. Apply the same ALARA principle on expenses for obvious economic reasons.

New rules exist for Paediatric radiology : Euratom 43/97 directives impose systematic dose measurement for children. From January 2006, each child will have his irradiation sheet. Guidelines are being published, they won't be coercive but indicative of good practice. **Imaging techniques are classified** into 5 categories, according to radiation risk :

- 0 0mSv Ultrasound, MRI
- I < 1 mSv Extremités, Chest Xay*
- II 1-5 mSv Spine, IVU, Skull CT
- III 5-10 mSv Body CT**, Baryum enema, Nuclear medicine
- IV >10 mSv PET Scan

*NB : A-P Chest XRy = 0.02 mSV= 2.4 days equivalent natural irradiation ; **Could be dramatically reduced with multislice scanners.

Different situations are being presented and discussed in a round table **Examinations** will be suggested as : Indicated as it is useful, Specialised as it is to be prescribed by a specialist after discussion ; Not indicated initially ; Not indicated routinely ; Not indicated.

CLINICAL VALIDATION OF HIGH-RESOLUTION FAST SPIN ECHO MR COLONOGRAPHY AFTER COLON DISTENSION WITH AIR. D. Bielen, H. Bosmans, D. Vanbeckevoort, S. Tejpar, P. Rutgeerts, G. Marchal University Hospital Gasthuisberg Leuven.

Purpose We have evaluated a multishot T1 weighted 2D turbo spin echo sequence for MR colonography (MRC) after distension of the colon with air for its feasibility and ability to detect colonic polyps or tumours.

Materials and Methods A randomly chosen patient population scheduled for conventional colonoscopy (n=21) was first submitted to MRC after classic bowel preparation with an electrolyte solution the same day. All patients were examined on a 1.5T Gyroscan system (Philips, Best, The Netherlands), using a multishot fast spin echo T1 weighted acquisition (T1wFSE) with a SENSE factor of 2. Images were acquired in both prone and supine position after the administration of a bowel relaxant. The degree of distension, amount of residual fluid and the delineation of the colonic wall was evaluated in different segments. Further the possibility for detection of polyps or other colonic lesions was evaluated.

Results and discussion The T1wFSE technique provided excellent image sharpness in 19/21 subjects. In 17/21 patients residual fluid obscured the colonic wall in different segments, either in prone or supine position, especially in ascending colon and caecum. Distension was sufficient for diagnosis in all segments, at least in prone or supine position. These findings are consistent with those for CT colonography. One lesion > 10 mm was missed and none of the 4 smaller lesions were visualized. There was one false positive lesion. Missing lesions can be due to inconsistency in slice positions due to the multishot character of the MR technique. Residual fluid may have obscured especially the smaller lesions. Further shortcomings are the limited coverage and the signal drop-off at the borders of the field of view.

Conclusion In order to make this MRC technique an alternative screening method for colonography, an improved patient preparation and a more practical acquisition technique should be worked out.

COMPUTED TOMOGRAPHIC COLONOGRAPHY AND COLONOSCOPY : TWO COMPLEMENTARY MEANS OF INVESTIGATION? A. Badaoui (1), D. Salovic (2), J. Gallez (1), N. Hachez (1), S. Noirhomme (1), N. Akle (1), J. Kirsch (2), A. Nakad (1). (1) Clinique Notre Dame - gastroenterology - Tournai ; (2) Clinique Notre Dame - Radiology - Tournai.

Aim : Colonoscopy and computed tomographic colonography (CTC) require a vigorous preparation. If CTC gives rise to suspect a lesion or in case of an incomplete colonoscopy, it should be possible to perform both investigations with less than 24 hours so as to benefit from a shared preparation. We studied the feasibility of this course of action.

Patients and methods : On a total of 500 colonoscopies and 60 CTCs performed over a period of 6 months, 47 patients benefited from having both investigations performed within 24 hours, with the same preparation. Twenty-three patients (4,6%) with incomplete colonoscopies benefited from a subsequent CTC because of neoplastic stenosis (3), non-passable sigmoid (5), and dolichocolon (15). Twenty-four CTCs (40%) required a colonoscopy because of discovery of polyps (16), suspicious colon segments (insufficient distension) (5) and non-contributory investigations (intolerance, residues...)(3).

Results : The second investigation was at all times possible and contributory in all patients without requiring a second preparation. Three out of the 16 polyps revealed during CTC (having a diameter of 5, 6, and 14 mm) were not objectified by colonoscopy (18,7%). Two out of the 5 suspicious segments described during CTC were normal in colonoscopy. The remaining 3 were compatible with benign inflammatory pathologies.

Conclusion : Pending on a good collaboration between radiologists, endoscopists and anesthetists, colonoscopy and CTC can be complementary, and can be performed using the same preparation within 24 hours. The association of these two methods can enhance the sensitivity of CTC and reduce colonoscopy-linked morbidity in case of an incomplete colonoscopy or when lesions are suspected during CTC.

MORBID OBESITY : “THE GOOD, THE FAT AND THE LEAKY”. K. de Jongh (1), E. Schepens (2), B. Op de Beeck (3), A. De Schepper (1), P. Parizel (1). (1) UZA Antwerpen ; (2) AZ VUB Brussel ; (3)UZA and AZ VUB.

Learning objectifs : To describe the different procedures of obese surgery (bariatric surgery). To illustrate the normal radiological findings. To outline the list of complications of the different kinds of bariatric surgery.

Background : Obesity and its comorbid disorders are leading causes of morbidity and premature mortality in developed countries. Mortality increases logarithmically for body mass indices that exceed 30. Only surgery results in sustained weight loss for seriously obese patients. Advancements in minimally invasive surgical techniques, specially laparoscopic techniques, have resulted in an expansion in obesity surgery over the last few years. It is important that radiologists be familiar with these operations to know the normal radiological findings and their complications.

Procedure details : To explain malabsorption-inducing and volume-reducing procedures of bariatric surgery, with their radiological findings. Describe the complications of the surgical procedures (leak, staple line failure, stenosis, band slippage) and their radiological components. Radiographic assessment is crucial in the management of weight loss and detection of post-operative complications.

Conclusion : Knowledge of normal radiological presentation of different types of bariatric surgery is mandatory in order to recognize complications at an early state.

LIFE THREATENING GASTROINTESTINAL BLOOD LOSS IN A PATIENT WITH CROHN DISEASE. Z. Yüksel (1), G. Veereman Wauters (1), J. Kunnen (3), T. Mahler (1), M. Van Caillie-Bertrand(1). (1) Queen Paola Children s hospital Antwerp ; (3) AZ Middelheim Antwerp.

Life threatening gastrointestinal blood loss is a rare complication in Crohn's disease. About 20 to 30 % of children with Crohn's disease present with rectal blood loss as first finding at diagnosis, mostly due to colonic involvement. Early localisation of the source of the bleeding is of great importance for the management and the outcome of the patient. We describe a male of 15 years old with Crohn's disease who presented with profuse rectal blood loss and weakness since a few hours. On admission the patient was in hypovolemic shock (pale, HR of 100 bpm and RR of 25 per minute, BP of 106/63 mm HG, Hb=9.8 g/dl,) and there were indication for active Crohn's disease (albumin of 23 g/l and PCDAI = 40). His current therapy was 32 mg/day prednisolone and 100 mg/day azathiopine. After stabilisation in the PICU, upper GI tract haemorrhage, colonic bleeding and bleeding from anal lesions were excluded by endoscopy. The corticotherapy was increased to 60 mg IV and azathiopine to 125 mg IV. The bleeding stopped. First relapse was two days later (D2), with profuse rectal blood loss (14% of the total body blood volume), hypovolemic shock and severe anaemia. After blood transfusion and IV hydration, selective mesenteric angiography demonstrated the localisation of the bleeding site from an ileal ulcer. Selective embolisation (with gelfoamstrips) of the distal braches of arteria mesenterica superior stopped the bleeding. On D5, life threatening rectal blood loss reoccurred (up to 19% of total blood volume) with hypotension. Surgical resection of inflamed intestine, including the bleeding site (30 cm of ileum including the ileocaecal valve) was performed. A third relapse (D9) massive rectal blood loss reoccurred. Selective angiography localised the bleeding from the arteria colica (at the anastomosis), embolisation with gelfoamstrips stopped the bleeding permanently. Profuse bleeding from the small intestinal tract is difficult to localize with endoscopy. Selective mesenteric angiography can be used to visualize acute small intestinal bleeding (one condition : bleeding rate = 1-2 ml/min) and for the localisation of non specific small intestinal ulceration. During angiography bleeding can be stopped with embolisation. The use of mesenteric angiography in Crohn's disease has been used since 1964 to demonstrate the extend of lesions (hyperaemia). Since 1974 it has also been used in Crohn's disease with rectal bleeding to demonstrate the source of the bleeding. Our conclusion is that when a patient with Crohn's disease presents with life threatening gastrointestinal blood loss, mesenteric angiography is recommended to locate and attempt to embolize the source of bleeding.

ENHANCED SONOGRAPHY OF THE LIVER : A VALUABLE METHOD FOR THE DETECTION OF LIVER METASTASES. E. Danse (1), P. Tréfois (1), E. Avalos (1), C. Dietrich (2), D. Fessler (2), W. Kratzer (2), K. Hauenstein (2), D. Hahn (2), D. Blank (2), D. Bunk (2), U. Vossas (2), D. Strobel (2), D. Koch (2), D. Oudkerk (3), C. Greiss (2). (1) Clin Univ. Saint-Luc, UCL, Belgium ; (2) Germany ; (3) Netherlands.

Aim of the study : To compare the sensitivity, the specificity and the accuracy of contrast-enhanced liver sonography for the detection of liver metastases in comparison with unenhanced sonography and triphasic CT.

Study design : An international multi-Center study including 12 investigators was conducted during a 10 month period. A dedicated study protocol was submitted and accepted by the ethic committee of each center. The study group was composed of patients with known primary extra-hepatic tumors and for whom liver metastases were to be excluded. In all cases, unenhanced sonography, contrast-enhanced sonography performed with Sonovue[®], tri-phasic CT and contrast MRI were performed. The findings of enhanced sonography were compared to those of unenhanced sonography and triphasic CT. Contrast MRI, follow up and biopsy (if performed) were considered as the gold standard method.

Results : From the 131 enrolled patients, 102 were considered as evaluable. Enhanced sonography was superior to unenhanced sonography for the detection of metastatic lesions ($p < 0.01$) and had higher accuracy for the detection of metastatic disease, in comparison with unenhanced sonography and triple phase spiral CT (91.2 % vs 81.4 % and 89.2 %, respectively).

Conclusion : Enhanced sonography can be considered as a valuable method for the detection of liver metastasis in patients with primary extrahepatic cancer.

ENHANCED SONOGRAPHY IN THE CHARACTERIZATION OF FOCAL LIVER LESIONS. E. Danse, P. Tréfois, L. Annet, E. Avalos, Y. Horsmans, J. Gigot, J. Baurain, P. Stärkel, I. Borbath, J. Lerut, B. Van Beers. Cliniques universitaires Saint-Luc, UCL, Belgium.

Aim of the study : To describe the findings observed with enhanced sonography in patients with focal liver lesions.

Material and Methods : 21 conventional sonographic examinations required to rule out a focal liver lesion were performed with intravenous injection of a new sonographic contrast agent (Sonovue[®]). The examinations were performed with dedicated machines equipped with specific software and using a low mechanical index. The examinations were divided in four parts, including unenhanced, arterial, portal, and late phases. The final diagnosis was based on CT, MRI, follow up or surgical findings. The final diagnoses were hepatocarcinomas (n= 9, including 6 untreated and 3 treated lesions), colic metastases (n= 5), metastases of melanomas (n=2), metastases of neuroendocrine tumors (n = 2), liver abscesses (n= 2), and simple liver cyst (n =1).

Results : In 19 of the 21 patients, the sonographic findings were confirmed. Untreated hepatocarcinomas, metastases of melanomas and of neuroendocrine tumors were seen as focal hypervascular lesions during the arterial phase. Treated hepatocarcinomas and abscesses were seen as hypovascular focal lesions during the arterial phase. During the portal phase, treated hepatocarcinomas, metastases of melanomas and of neuroendocrine tumors and liver abscesses were hypovascular. A peripheral hypervascular rim was observed during the portal phase in treated hepatocarcinomas, neuroendocrine metastases and liver abscesses. During the late phase, metastases of melanomas and liver abscesses appeared as hypovascular lesions. Cysts were avascular during all the phases.

TUBERCULOSIS OF THE PANCREAS : CT AND MRI FEATURES. A. De Backer (1), K.J Mortelé (2), P. Bomans (1), S. Bourgeois (1), M. Osselaer (1), B.L De Keulenaer (3), M. Kockx (1). (1) Antwerp, Belgium ; (2) Boston (USA) ; (3) Rocklands (AUS).

Objective. The purpose of this study was to describe the CT and MRI features of tuberculosis of the pancreas.

Materials and methods : We reviewed the files of three patients with tuberculosis of the pancreas. CT scans and MRI findings were available for two and three patients respectively.

Results : In two patients, involvement was characterized by a sharply delineated heterogeneous mass located in the pancreatic head, showing peripheral and central areas of contrast enhancement. The size of the lesion was 4 and 2.5 cm, respectively. Non-enhanced fat-suppressed T1-weighted images showed hypointense lesions compared to normal pancreatic tissue and a heterogeneous mass with mixed hypo- and hyperintensities on T2-weighted images. In these patients, the common bile duct and main pancreatic duct were normal. In one patient, involvement resulted in diffuse enlargement of the pancreas with diffuse narrowing of the main pancreatic duct. On MRI, signal abnormalities were characterized by hypointensity and hyperintensity on fat-suppressed T1-weighted and T2-weighted images, respectively. Contrast enhanced images showed a slightly heterogeneous enhancement of the pancreas. In all patients, signs of miliary tuberculosis were present and characterized by abdominal lymphadenopathy and pulmonary involvement.

Conclusion : The presence of a mass in the pancreas or diffuse enlargement of the gland in patients with miliary tuberculosis or other types of abdominal tuberculosis should raise the possibility of tuberculous involvement of the pancreas.

GENETIC TESTING IN IBD. WHERE DO WE STAND? S.Vermeire – Gastroenterology Department – University Hospital Leuven

The first and so far only gene identified in Crohn's disease (CD) is NOD2/CARD15. CARD15 encodes a protein involved in the host's first line defense against microbial invasion, and leads to apoptosis by the mediation of NFκB. Three major variants have been identified of which the frameshift mutation Leu1007insC leads to a truncated Card15 protein with impaired ability to recognize microbial components. The relevance of CARD15 genetic testing in clinical practice is however still modest. The prevalence of CARD15 mutations is 30-45% in European and North-American Caucasian IBD patients. However, in the Japanese and African-American IBD population, CARD15 mutations are absent and in Scandinavian countries significantly less CARD15 variants are found. CARD15 variants are also found in 20% of healthy individuals. Therefore the absence of a mutation in an unaffected individual does not exclude the development of the disease, nor does the presence of a mutation necessarily mean a diagnosis of CD. Also screening unaffected relatives of CD patients is not recommended until preventive strategies are available. Regarding the phenotypic expression of CARD15 mutations, current data almost unanimously show an association with small bowel involvement. More studies are needed to know if CARD15 mutations are also associated with a fibrostenotic behavior of the disease. If CARD15 variants would predict a more severe disease course, then a more aggressive treatment would be justified in these patients. Genes also interfere with the metabolising pathways of drugs and may influence clinical response and drug-related toxicity. The clinical relevance of pharmacogenetics have been illustrated for azathioprine (AZA). One of the metabolic pathways of AZA occurs through the enzyme thiopurine methyl transferase (TPMT), which activity is genetically determined. Measurement of TPMT genotypes/activity and of AZA metabolite 6-thio guanine nucleotide are clinically useful and predict myelo- and hepatotoxicity. The search for the IBD genes is rapidly progressing as we speak and other genes will undoubtedly follow. Also the field of pharmacogenetics is being intensively explored and will hopefully lead to a more individually-tailored therapeutic approach of our patients.

NEW INSIGHTS IN THE FUNCTION OF LYMPHOCYTES IN IBD. M.Allez. Service de Gastroentérologie et INSERM U396, Hôpital Saint-Louis, Paris.

The mucosa associated lymphoid tissue has the task to recognize harmful pathogens which attack the epithelial layer, in order to mount an effective immune response. This system must also be able to tolerate the intestinal microenvironment and despite the immune stimulus, the intestine remains in a state of controlled inflammation. There are many levels which by the immune response can be regulated including antigen elimination, altered antigen presentation, depletion of activating cytokines, production of regulatory cytokines, apoptosis (of activated immune cells), or active suppression. A number of experimental systems show that altered regulation of intestinal T cell function can result in chronic intestinal inflammation. Defects in the generation and/or activation of regulatory T cells may favor the uncontrolled inflammation seen in IBD. Distinct regulatory T cells have been described within the CD4+ and CD8+ populations, many of which reside in the intestinal mucosa. Works in different systems suggest that the intestine is a fertile environment for their growth and activity. How these different T regulatory subsets are locally activated and/or expanded remains poorly understood. There is growing evidence that intestinal epithelial cells have the ability to present antigens to mucosal lymphocytes, and may activate both effector and regulatory T cells. A unique population of CD8+ regulatory T cells, called CD8+ TrE, is activated through a unique complex expressed on intestinal epithelial cells. There is a lack of activation of CD8+ TrE in IBD.

LONG TERM SAFETY OF IMMUNOMODULATORY THERAPY IN INFLAMMATORY BOWEL DISEASES.
E. Louis. Gastro Unit CHU Liège.

Immunomodulatory therapies have been increasingly used since the beginning of the nineties in inflammatory bowel disease (IBD). They are clearly associated with clinical benefits, including prolonged remission, decreased glucocorticoid use, and improved quality of life. However, as it could have been expected, they do not cure the disease and a significant number of relapses occur over time when stopping treatment even after prolonged therapy. Therefore, with this increase in long term treatment with immunomodulatory drugs in IBD, safety may become a particularly important issue. The main feared long term complications are : cancers and particularly lymphomas, infections and other side effects more specific of some of these drugs. No increased risk of solid tumors has been detected with any of these drugs. For lymphomas, a slightly increased risk may exist with thiopurine derivatives, essentially Epstein-Barr virus-positive lymphomas. Globally however, studies have clearly shown that benefits outweigh the risk of lymphoma with these drugs. A few cases of lymphomas have also been reported in Crohn's disease patients treated with infliximab. However, no increased risk has been shown so far. Severe infections are probably the most common long term safety problem with immunomodulatory drugs in IBD. However no study has specifically evaluated the relative risk of severe infection with these drugs in IBD. Fatal or life threatening opportunistic or more trivial infections may occur with these drugs. Either viral or parasitic infections have been reported. The association between tuberculosis reactivation and infliximab treatment has been particularly well documented and has given rise to important and precise guidelines. Controversial data have been recently published about safety of long term 6-thioguanine treatment in IBD. Particularly, the description of a large proportion of nodular regenerative hyperplasia clearly emphasizes the need for controlled evaluation before further use of this drug. On the opposite, long term data with methotrexate beyond a cumulative dose of 1500 mg have been reassuring. Finally the development of biological signs of auto-immunity is frequent in long term infliximab treatment. The long term impact of this auto-immunity remains to be clarified.

FUTURE MEDICAL APPROACHES FOR IBD. G.D'Haens, Bonheiden, KUL.

The efficacy of available therapies for inflammatory bowel disease has improved significantly in recent years. In patients with active and aggressive disease the classic approach consists in a combination of treatment to 'induce' remission with a second treatment to 'maintain' remission. For Crohn's disease, the most potent agents to induce remission are corticosteroids and infliximab, whereas maintenance agents include azathioprine, methotrexate and infliximab. For ulcerative colitis, corticosteroids and cyclosporine are the best induction agents, whereas only azathioprine and 6-mercaptopurine have proven maintenance benefits. It is not unlikely that in the years ahead the use of corticosteroids for Crohn's disease, given their poor adverse event profile, will diminish significantly. Now that we are beginning to collect strong data on the long-term safety of infliximab and given the efficacy of this treatment in the majority of patients, we might even see a change in paradigms where infliximab is introduced earlier in the course of the disease, in an attempt to try and prevent complications such as stenosis and fistula formation. Prospective trials looking at this approach are being performed. Besides infliximab, a whole range of new 'biological therapies' for IBD is being investigated. Anti-TNF-antibodies, which are fully humanized and may lead to fewer infusion reactions have already been developed and are being tested in trials. Other proinflammatory cytokines such as IL-12, IFN-g and IL-6 can also be blocked with novel antibodies with which preliminary results are promising. Furthermore, several mechanisms of recruitment of inflammatory cells via the vascular endothelium are being explored. In this field, Natalizumab (Antegren) is the most promising agent for Crohn's disease at the time being. For ulcerative colitis, several targets are under study : the Act-1 trial with infliximab for refractory ulcerative colitis, has reached the end of recruitment. Results are eagerly being awaited. Millennium developed an antibody against the combination of the adhesion molecules $\alpha 4$ and $\beta 7$, which is highly specific for the gut. Finally, daclizumab (Zenapax), which binds to the α -chain of the IL-2 receptor expressed by activated T cells, showed promising results in a pilot trial. In summary, the advent of biologic agents has provided great research opportunities to unravel the pathogenesis of IBD. The safety profile of these agents looks all together reassuring. The future of IBD management will, as a consequence, not only be more refined, but above all highly more effective.

CLINICAL RELEVANCES OF IBD IN CHILDHOOD -INFLAMMATORY BOWEL DISEASE IN CHILDREN AND ADOLESCENTS. H.A. Büller, ErasmusMC, Sophia Children's Hospital, Rotterdam, The Netherlands.

The widespread adoption of routine use of colonoscopy and oesophagogastroduodenoscopy (OGD) with histology, even in very young children has resulted in better epidemiological data regarding disease extent and severity in children and adolescents. In the past 20 years there is a clear increase in the incidence of IBD from about 2 per 100.000 children <16 years of age per year to 5.2 and in Scandinavia even up to 7.

Clinical features. In recent studies the classic triad of diarrhoea, weight loss and abdominal pain for CD at presentation was only found in 25% of new cases, while 44% had no complaints of diarrhoea at all at presentation. In very young children failure to thrive, lethargy or chronic fever are distinguishing features for CD, whereas bloody stools is the characteristic symptom for UC. European consensus has been achieved regarding the work-up of children suspected of IBD. The initial work-up should include full colonoscopy with ileal inspection and full length histology, OGD with histology at defined sites and barium follow through.

Complications of disease. IBD is a risk factor for osteoporosis and is related to duration of steroid use and disease activity. Prevention of osteoporosis in children should be aimed at adequate nutrition, control of inflammation, exercise and attention for Vitamin D and calcium intake. The cumulative incidence risk of cancer in children with UC starting before the age of 14 years is 50% by the time they are 50 years old. Prophylactic colectomy is therefore a matter of intense debate.

Etiology. Much attention has been paid to delineating genetic susceptibility but limited emphasis has been given to potential environmental risk factors, such as dietary factors or infection influencing the risk for developing IBD. Clearly there is an increased risk associated with migration to western societies, as shown by hispanics and asians in the USA and the UK. Young children form an ideal group to delineate these factors because of the absence of possible confounding influences.

Treatment. Conventional therapy is based on a therapeutic triangle in which "mild drugs" 5-aminosalicylates is the first line therapy for mild disease activity. In more severe cases corticosteroids are added, followed by immunosuppressives such as azathioprine or 6-MP and biologicals such as infliximab. Successful management of IBD in children and adolescents should be aimed at endoscopic or mucosal healing, given the longstanding disease with increased risk of malignant deterioration.

THE ROLE OF CT-SCAN AND MRI IN THE EVALUATION OF LUMINAL AND FISTULIZING CD. B. Op de Beeck. Antwerp UA.

Accurate assessment of intestinal complications of Crohn's disease (CD) is extremely important. The accuracy of radiographic diagnosis of internal fistulae and abscesses complicating CD is still debated and requires further investigation. Whatever method of radiologic investigation is employed, it should be targeted to answer questions relevant to patient management. Multislice computed tomography (MSCT) of the small intestine is superior to conventional enteroclysis, especially in the diagnosis of mesenteric or other extraintestinal disease. As a side effect, the colon is assessed in the same examination. Radiation dose is less in MSCT than in conventional fluoroscopy. MSCT can be performed as an alternative or adjunct to colonoscopy, if endoscopic access is restricted. Virtual endoscopy is a recently introduced technique which can provide an addition to the sectional findings. CT and MRI identify extent, severity and intestinal complications with adequate diagnostic accuracy. Both techniques possess the potential for replacing enteroclysis in the work-up of CD. Enteroclysis should be reserved for the work-up of complex fistula systems. Good correlation has been reported between CT or MRI findings and disease activity. These results are in contrast to barium studies, which have limited correlation with symptomatology or response to therapy. Moreover, the potential harm of radiation exposure from serial barium examinations in pregnant women and patients of reproductive age is not inconsequential. The use of MRI in the work-up of patients with CD cannot be generally recommended from an economical perspective, but results of sensitivity analysis suggest that in patients with high prevalence of complications, MRI becomes as cost-effective as enteroclysis.

OPTIMAL MANAGEMENT OF PERIANAL FISTULAS IN CROHN'S DISEASE. M.A. Kamm. Gastroenterology and Medicine, St Mark's Hospital, London, England.

Perianal fistulas occur in a quarter to half of all patients with Crohn's disease at some time in their illness. An association of perianal Crohn's disease with a susceptibility locus on chromosome 5 has recently been described. Fistulas derive from the anal glands then track away from the anal canal. Their complexity determines the surgical approach. Complicated perianal disease is associated with increased malignant risk. Treatment is most effective when antibacterial, immune suppression, and physical factors such as drainage are addressed. Surgical treatment includes abscess drainage, use of a non-dissolving thread ("seton"), laying open of superficial fistulas, and coring out of deeper fistula. More extensive surgery, with sphincter muscle division, can lead to impaired continence. Faecal diversion provides only temporary remission. In a study from St Mark's on long term follow-up 70 percent of patients had healed, after a median of 2.6 years and three surgical treatments. Complex fistulas often required stoma formation, resection, or proctectomy. Metronidazole, ciprofloxacin, cyclosporin and tacrolimus are useful in the short term. Azathioprine reduces inflammation, discharge and discomfort. Infliximab rapidly heals a majority of patients short term, and about a third of patients at one year. MRI scanning helps exclude abscesses, assesses deep healing, and may help determine duration of treatment. The treatment of Crohn's fistulas is the an area par excellence where co-operation between surgeon and gastroenterologist is likely to lead to greatest therapeutic success.

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New endoscopic tools in the study of IBD and management of suspicious lesions. A. Van Gossum, Dept of Gastroenterology, ULB, Hôpital Erasme.

It is well accepted that patients with IBD bear a potential higher risk of developing colorectal cancer (CRC), mainly in ulcerative colitis. Risk-factors include disease duration, extensive mucosal involvement, concomitant primary sclerosing cholangitis, familial history of CRC. A recent study has shown that flat low-grade dysplasia during ulcerative colitis surveillance is a strong predictor of progression to advanced neoplasia (1). Observational evidence suggests (but without evidence) that surveillance colonoscopy reduces the mortality rate of CRC in ulcerative colitis. The safest approach would be to take at least 30-40 biopsies and to obtain a biopsy of any masses (2). Recent techniques have been developed in order to increase the efficacy of an endoscopic surveillance. Methylene blue-aided chromoendoscopy seems to be a novel tool for the early detection of intraepithelial neoplasias and CRC (3). Fluorescence endoscopy after 5-ALA sensitization (local or systemic) appears also as a possible tool to visualize dysplastic lesions (4). An other challenge is the therapeutic option in case of mass : colectomy or polypectomy ? Polypectomy could be proposed for lesions including polyps on a distinct stalk, sporadic adenoma-like polyps proximal to the area of colitis and adenoma-like masses (5,6).

(1) *Ullman T et al, Gastroenterology 2003 ; 125 : 1311-9.*

(2) *Bernstein C, IBD 1998 ; 90 : 2106-14.*

(3) *Kiesslich R et al, Gastroenterology 2003 ; 124 : 880-8.*

(4) *Messmann H et al, Gut 2003 ; 52 : 1003-7.*

(5) *Engelsgjerd M et al, Gastroenterology 1999 ; 117 : 1288.*

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THE EFFECTS OF TREATMENT IN IBD. R. Riddell, Lab Medicine and Pathobiology, University of Toronto, Mount Sinai Hospital, Toronto, Ontario, Canada.

Therapy in IBD is directed to promote healing and can occur spontaneously or following medical or surgical therapy. Indeed, the high rate of placebo responses attests to the difficulty in carrying out meaningful clinical trials in IBD, often being in the 30% plus range. Surgery is reserved for relief of symptoms not readily managed by other forms of therapy but bypass operations in Crohn's disease (CD) do promote healing, but can also result in diversion disease and pouchitis. Colectomy may result in improvement of the upper GI (gastroduodenal) involvement seen in ulcerative colitis (UC) especially in the pediatric population.

Medical therapy is intended to result in improvement of symptoms by decreasing inflammation. However, the relationship between pathology, endoscopy and symptoms, while showing correlation in large series, may not hold too well in individual patients. The correlation is seen better in ulcerative colitis (UC) than in CD, as are the effects of therapy. Most forms of therapy result in a) decrease in acute inflammation and healing erosions and ulcers in the short term. b) chronic inflammation that may resolve in the long-term c) possible resolution of architectural distortion. However where ulcers destroy the muscularis mucosae this is healed by fibromuscular proliferation and duplication of muscularis mucosae that can result in strictures. With healing, the reduction in acute and ultimately chronic inflammatory cells is accompanied by reduction in inflammatory molecules, lymphokines and cytokines associated with them. Drugs that block the inflammatory cascade or down regulate inflammation can promote healing, adding to the evidence that IBD may be a failure of the individual to down regulate an inflammatory response. Medical therapy may also reduce the long-term risk of colorectal carcinoma, but nonsteroidal (NSAIDs) and immunosuppressants such as mycophenolate mofetil may result in colitis or exacerbation of underlying IBD.

PREVENTION AND CHEMOPROPHYLAXIS OF COLORECTAL CANCER IN IBD. G. Van Assche, P. Rutgeerts, Division of Gastroenterology, University Hospitals Leuven, Belgium.

Even if colorectal cancer (CRC) associated with inflammatory bowel diseases (IBD) represents only 2% of CRC cases, it is of great concern to the physicians caring for IBD patients. Colitis associated dysplasia and subsequent CRC is associated with longstanding ulcerative colitis (UC) but also with Crohn's colitis. Longstanding disease (and young age at onset), extensive disease, primary sclerosing cholangitis (PSC) and genetic or familial background have all been recognized to increase the risk of CRC¹. Prevention of CRC consists of three complementary strategies. 1. Endoscopic and histological screening of patients at risk ; 2. Chemoprevention with maintenance therapy ; 3. Surgical prevention, i.e. total colectomy in UC and resection of strictured segments in Crohn's colitis. Guidelines for endoscopic surveillance differ between continents and countries, but it is widely accepted that high-risk patients are eligible for endoscopy of the involved colonic segments with multiple biopsies at regular intervals. Dysplasia, particularly in areas without active inflammation, warrants total colectomy in UC. The interest in chemoprevention in IBD colitis has originated from studies in familial polyposis with NSAIDs and salicylates. Aminosalicylates have been the cornerstone of maintenance therapy for UC and recent reports suggest that they have a role in chemoprevention of CRC. Indeed, case-control studies from North America and the UK have shown a decrease of the CRC incidence by 60 to 80%^{2,3}. Interestingly, in the largest of these studies frequent visits to the treating physician were equally effective at reducing the CRC risk suggesting that patient compliance is of paramount importance. For the specific population of IBD patients with concomitant PSC ursolic acid has been shown to reduce the risk of CRC when used at high doses (20 mg/kg)⁴.

(1) Ekblom et al. *N Eng J Med* 1990 ; 323 : 1228-1233.

(2) Eaden. *Aliment Pharmacol Ther* 2000 ;14 :145-152.

(3) Moody et al. *Eur J Gastroenterol Hepatol* 1996 ;8 :1179-1183.

(4) Tung et al. *Ann Int Med* 2001 ; 134 : 89-95

**XVth Belgian Week of Gastroenterology
February 12-14, 2004**

ABSTRACTS

A01 — A25	Belgian Association for the Study of the Liver (BASL)
B01 — B20	Research Group “Gastrointestinal Regulatory Mechanisms (OG-NFWO)”
C01 — C10	Belgian <i>Helicobacter Pylori</i> Study Group
D01 — D73	Joint Meeting of Gastroenterology
P01 — P11	Gastro-intestinal Pathology Club
N01 — N08	Research Group of Clinical Nutrition and Metabolism (SBNC and VVKVM)
G01 — G08	Belgian Group of Pediatric Gastroenterology and Nutrition
R01 — R08	Research Group “Digestive and Abdominal Imaging”
S01 — S10	Symposium of the six societies “Recent Advances in the Management of IBD”

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