ABSTRACTS

XVIIth Belgian Week of Gastroenterology
2005

- A 01 -

HIGH DENSITY LIPOPROTEINS FACILITATE HEPATITIS C VIRUS ENTRY THROUGH INTERACTION WITH THE SCAVENGER RECEPTOR CLASS B TYPE I. A. Op De Beeck (1), C. Voisset (2), N. Callens (2), E. Blanchard (2), J. Dubuisson (2), N. Vu-Dac (2). (1) Laboratoire de Virologie Moleculaire ULB Hopital Erasme, Bruxelles, Belgique & CNRS-UPR2511 Institut de Biologie de Lille, France ; (2) CNRS-UPR2511 Institut de Biologie de Lille, France.

The scavenger receptor class B type I (SR-BI) has recently been shown to interact with hepatitis C virus (HCV) envelope glycoprotein E2, suggesting that it might be involved at some step of HCV entry into host cells. However, due to the absence of a cell culture system to efficiently amplify HCV, the contribution of SR-BI to HCV entry is still an open issue. Here, we sought to determine how high density lipoproteins (HDL), the natural ligand of SR-BI, affect HCV entry. By using the recently described infectious HCV pseudotyped particles (HCVpp) that display functional E1E2 glycoprotein complexes, we showed that HDL are able to markedly enhance HCVpp entry. We did not find any evidence of HDL association with HCVpp, suggesting that HCVpp do not enter into target cells using HDL as a carrier to bind to its receptor. Interestingly, lipid-free ApoAI and ApoAII, the major HDL apolipoproteins, were unable to enhance HCVpp infectivity, suggesting a role for lipid transfer in facilitating HCVpp entry. Silencing of SR-BI expression in target cells by RNA interference markedly reduced HDL-mediated enhancement of HCVpp entry. In addition, enhancement of HCVpp entry was also suppressed when SR-BI binding region on E2 glycoprotein was deleted. Altogether, these data indicate that HDL-mediated enhancement of HCVpp entry involves a complex interplay between SR-BI, HDL and HCV envelope glycoproteins, and they highlight the active role of HDL in HCV entry.

- A 02 -

ASYMMETRIC DIMETHYLARGINE (ADMA) IS INVOLVED IN PORTAL HYPERTENSION OF BILIARY BUT NOT OF TOXIC CIRRHOTIC RATS. W. Laleman (1), A. Omasta (1), M. Vandecasteele (1), M. Zeegers (1), I. Vander Elst (1), T. Roskams (2), J. Fevery (1), F. Nevens (1). (1) Hepatology, (2) Histopathology, UZ Gasthuisberg, Leuven.

Background : Reduced intrahepatic endothelial nitric oxide synthase (eNOS) activity is involved in the pathogenesis of cirrhotic portal hypertension (PHT). We aimed at evaluating whether the cause of reduced NOS activity differs depending on the etiology of cirrhosis and whether asymmetric dimethylarginine (ADMA), a putative endogenous NOS inhibitor, could be involved.
Methods : We evaluated NOS activity and eNOS protein levels in 2 cirrhotic rat models of PHT, CCl4 and bile duct excised (BDE). Sham-operated rats served as controls (total n = 30). Plasma ADMA levels were measured by HPLC. The intrahepatic vasoactive properties of ADMA were evaluated by performing concentration-effect curves to acetylcholine after precontraction with methoxamine in a liver perfusion model, preincubated either with vehicle, ADMA, symmetric dimethylarginine (SDMA, the vasoinactive stereoisomer of ADMA) and the NOS-inhbitor L-NAME. Nitrate/nitrite (NOx) production was determined in samples of the perfusate.
Results : CCl_4 and BDE cirrhotic rats showed significantly decreased hepatic NOS activity (2.8 ± 0.3 for CCl_4 and 1.9 ± 0.1 for BDE vs 4.1 ± 0.3 pmol/min/mg protein for sham-operated rats) but only in CCl_4-rats hepatic eNOS protein levels (65 ± 9 % vs 98 ± 2 % for controls, $P < 0.05$) and semi-quantitative assesment of immunoreactivity ($P < 0.05$ vs BDE and control rats) were reduced. In contrast, normal eNOS protein levels in BDE rats were associated with decreased NOS activity. Significantly higher ADMA levels were found only in BDE rats (2.92 ± 0.59 µM vs 0.69 ± 0.37 µM for controls and 0.82 ± 0.29 µM for CCl_4 rats, $P < 0.05$). In the isolated liver perfusion model, livers incubated with ADMA, when compared to vehicle, exhibited markedly less relaxation to acetylcholine (at 10^{-5} M : -2.5 ± 2.4 % vs -16.9 ± 2.3 % for vehicle, $P = 0.002$), which was associated with decreased NOx production (-29.6 ± 3.1 nM vs -0.4 ± 5 nM for vehicle, $P < 0.05$). A similar effect on endothelial function and NOx production as ADMA was observed for L-NAME, while SDMA was comparable to vehicle.
Conclusion : The etiopathology of NOS dysfunction depends on the etiology of cirrhosis. In CCl_4-cirrhosis, a decreased enzyme level is responsible for decreased NOS activity, while in biliary cirrhosis NOS dysfunction might be caused by an endogenous NOS inhibitor, ADMA.

- A 03 -

PROGRESSION FROM MILD FIBROSIS TO CIRRHOSIS IS ASSOCIATED WITH INCREASED BCL-2 AND PIAS3 AND DECREASED STAT3 AND CYCLIND1 EXPRESSION IN HEPATITIS C INFECTED LIVERS. P. Starkel, C. De Saeger, I. Leclercq, Y. Horsmans. Department of Gastroenterology, St. Luc University Hospital, Brussels, Belgium.

Background : In vitro and animal data suggest that HCV proteins might interfere with Stat3 signalling. However, only limited data are available concerning Stat3 expression and its association with cellular proliferation and apoptosis in human liver.
Aim : We examined expression of Stat3 and proteins involved in controlling Stat3 signalling as well as cell cycle and apoptosis markers in human livers infected with HCV at various stages of fibrosis progression.
Methods : Human liver biopsies matched for inflammatory scores without fibrosis or with mild fibrosis or established cirrhosis were examined for expression of Stat3, Socs3, Pias3, cyclin D1, Bcl-2, and Bax. Protein expression in liver homogenates was determined by Western blotting and Mrna levels by quantitative PCR.
Results : Stat3 protein expression started to decreased with appearance of fibrosis and was significantly lower in established cirrhosis compared to liver biopsies without fibrosis. In addition, Pias3 protein and Mrna expression increased progressively with the progression from mild fibrosis to cirrhosis whereas Socs3 Mrna dropped only significantly once cirrhosis has been established. In parallel, cyclin D1 protein expression decreased and Bcl-2 increased progressively with appearance of fibrosis both being significantly different in established cirrhosis compared to biopsies without fibrosis. Cyclin D1 correlated significantly with Stat3 expression ($R^2 = 0.61$; $p < 0.001$) whereas no correlation was found between Bcl-2 and Stat3. Bax expression did not change significantly.
Conclusion : Disturbances in Stat3 signalling might contribute to progression from mild fibrosis to cirrhosis in HCV infected livers possibly through disturbed cell cycle progression that is only insufficiently compensated by activation of anti-apoptotic pathways.

-A 04 -

INHIBITION OF MEMBRANE ANCHORAGE OF THE RAS ONCOPROTEIN REDUCES HEPATOCYTE PROLIFERATION IN RATS AFTER PARTIAL HEPATECTOMY. A. Da Silva (1), C. De Saeger (1), I. Leclercq (1), A. Saliez (2), Y. Horsmans (1), P. Starkel (1). (1) Department of Gastroenterology, St. Luc University Hospital ; (2) Laboratoty of Experimental Surgery, Université Catholique de Louvain, Brussels, Belgium.

Background : The Ras oncoprotein seems to be over-expressed and/or mutated in hepato-cellular carcinoma (HCC). Studies in cell lines suggest that the ability of Ras to promote cell differentiation and proliferation is prevented by inhibiting its membrane anchorage for example after administration of the ras antagonist S-Farnesylthiosalycilic acid (FTS). In addition, Ras mediated activation of the MAPkinase pathway seems to play a role in promoting cell proliferation.
Aims : To evaluate in vivo the impact of the inhibition of Ras membrane anchorage, using treatment with FTS, on hepatocyte proliferation in rats after partial hepatectomy (PH).
Methods : Male Wistar rats were administered FTS intraperitoneally (50mg/kg, 1,8,16h after PH) and sacrificed 12 or 24 hours after PH. BrdU incorporation was visualized by immunohistochemisty and quantified by flow cytometry. Protein expression in different cell fractions was analysed by Western blotting. Real time PCR was used for mRNA expression.
Results : FTS treatment induced a significant reduction in BrdU incorporation and PCNA protein expression after PH in hepatocytes. Unlike control rats, the Ras protein was found in substantial amounts in the cytosol of FTS-treated animals suggesting the inhibition of Ras membrane anchorage that ultimately results in inactivation of Ras. In addition, no Raf membrane recruitment and phosporylation was observed in the membrane fractions of FTS-treated rats and consequently phosphorylation of Erk1/2 located down-stream in the ras-raf signalling pathway was found to be reduced, thereby, confirming the functional inhibition of Ras. Amplification of mRNA by real time PCR showed a similar increase in Ras mRNA after PH in control and FTS-treated animals suggesting that FTS does not affect Ras mRNA expression but only the mature protein.
Conclusions : Taken together, these observations show that the functional inhibition of Ras, by FTS, results in a significant reduction in liver cell proliferation even after a strong and highly synchronized proliferation stimulus such as PH. The inhibitory effect is at least in part mediated by inhibition of ras-dependent Raf-MAPkinase-ERK signalling. Therefore, it seems worthwhile to evaluate the impact of Ras inhibition on carcinogenesis and treatment of HCC.

- A 05 -

PROTECTIVE ROLE OF CCR5 IN CONCANAVALIN A-INDUCED HEPATITIS IN MICE. C. Moreno (1), T. Gustot (1), C. Nicaise (1), E. Quertinmont (1), N. Nagy (2), M. Parmentier (3), O. Le Moine (1), J. Devière (1), H. Louis (1). (1) Laboratory of experimental gastroenterology, ULB ; (2) Division of Pathology, Erasme Hospital, ULB ; (3) IRIBHN, ULB.

Background and aim : Experimental T cell-mediated hepatitis induced by Concanavalin A (Con A) involves the production of different cytokines and chemokines, and is characterized by leukocyte infiltration. The chemokine receptor CCR5 and its ligands (CCL3/MIP-1 ± , CCL4/MIP-1², CCL5/RANTES, CCL8/MCP2) regulate leukocyte chemotaxis and activation. However, the role of CCR5 in experimental hepatitis remains poorly understood.
Methods : Experimental hepatitis was induced by intravenous Con A injection in CCR5-deficient ($CCR5^{-/-}$) or wild-type (WT) mice. In vivo neutralization of CCR5 ligands with monoclonal antibodies (mAb) before Con A challenge was also performed in WT mice. Mortality rate was assessed and liver injury was evaluated by serum alanine transaminase (ALT) measurement and by histology 8 hours after induction of hepatitis. CCR5 expression on liver mononuclear cells was measured by flow cytometry analysis. Serum levels of proinflammatory cytokines and CCR5 ligands hepatic Mrna expression were also determined.
Results : An increase in CCR5+ liver mononuclear cells was observed after Con A challenge. Hepatic Mrna expression and serum levels of CCL3/MIP-1 ± and CCL4/MIP-1¸ were detected early after Con A injection while the increase in CCL5/RANTES and CCL8/MCP-2 Mrna expression occurred later. While all WT mice survived following 10 mg/kg Con A injection, mortality reached 80 % in $CCR5^{-/-}$ mice. A striking difference in liver injury was also observed after 5mg/kg Con A injection (ALT 4147 vs 63,5 U/L in $CCR5^{-/-}$ vs WT mice). IL-4, TNF-± and CCR5 ligands serum levels were significantly increased in $CCR5^{-/-}$ mice when compared to WT mice while IFN-³ serum level was not different between both groups. Pretreatment with anti-CCL3, anti-CCL4 or anti-CCL5 mAb did not modify the extent of Con A-induced liver injury.
Conclusions : Our data suggest that CCR5 plays a protective role during experimental hepatitis induced by Con A. Immunomodulation through control of IL-4 and TNF- ± production is likely to be one of the protective mechanisms.

- A 06 -

ROLE OF HBV OR HCV PROTEINS ON INDUCTION OF ANTI-OXIDANT ENZYMES IN LIVER CELLS : DEVELOPMENT OF AN IN VITRO METHOD USING TRANSFECTED HEPG2 CELLS. L. Van Aelst, T. Crabbé, T. Severi, C. Verslype, J.F van Pelt. Labo Hepatology, UZ Gasthuisberg, Herestraat 49, B 3000 Leuven, Belgium.

Introduction and aim : A number of processes generate radicals. These radicals can have a signaling function but can also damage the cell. Therefore, the cell produces enzymes that can convert radicals to less reactive compounds. These enzymes so help to maintain the redox-balance within the cell. The aim of the present study was to investigate whether expression of HBV or HCV proteins could induce oxidative stress. The second question was whether viral proteins could stimulate or induce enzymes that are capable to decrease radicals.
Materials and methods : The esterified-form of the dye (DCFH-DA) can penetrate the cell, where it is transformed to DCFH and accumulates in the cell. Oxidative radicals convert DCFH into DCF (fluorescent) and this signal is a measure for oxidative reactions in the cell (*Hempel SL et al. Free Radic.Biol.Med. (1999)27(1-2) ; 146-159*). We wanted to study the level of oxidative radicals in cell lines that express HBV or HCV proteins (*van Pelt JF et al. Cancer Lett (2004) 209 ;197-205*). Therefore we optimized the method and investigated the role of the medium on the oxidation of DCFH. Secondly, we wanted to investigate the sensitivity in these cells for exposure to radicals (eg H2O2 or NO). Accelerated decomposition of oxidative radicals (resulting in slower formation of DCF) will be an indication for the up regulation of anti-oxidant enzymes by viral proteins.
Results and discussion : **A)** On the method : we found that serum interferes when cells are exposed to H_2O_2, NO, Ethanol or Fe^{2+}. **B)** In cell lines stably transfected with either HBx, HBsAg or HCV core protein, the formation of oxidative stress did not differ significantly from control HepG2 cells. **C)** Hepatitis transfected cells were less sensitive to exposure to H_2O_2 than controls. The present observations are in agreement with the study in HepG2AD38 cells where we found that HBV replication can temporary shift the redox-balance (more oxidized GSSG/GSH) and the induction of SOD, FMO, MT and other anti-oxidant enzymes (*Severi et al., manuscript in preparation*). This suggests that the virus can induce some level of protection in the cell against immunological attacks and so promoting its own survival. With this method we hope to study the interaction between pro- and anti-oxidant compounds in liver cells in relation to hepatitis virus.

- A 07 -

AN INDUCIBLE CELL CULTURE MODEL OF HEPAD38 CELLS TO STUDY THE EFFECTS OF HEPATITIS B VIRUS REPLICATION ON OXIDATIVE STRESS, GENE EXPRESSION AND INDUCTION OF GENETIC CHANGES. T. Severi (1), CH. Ying (2), J. Vermeesch (3), M. Zeegers (1), A. Van Lommel (5), R. Servaes (1), J. Neyts (2), J. Fevery (1), J.F van Pelt (1). (1) Labo Hepatology ; (2) Labo Virology, REGA institute, Fact Medicine ; (3) Dpt. Human Genetics, (5) Dpt. Pathology, Univ Hospital Gasthuisberg, Leuven, Belgium.

We investigated whether HBV replication in liver cells can give rise to genetic changes in the hepatocytes cell as a mechanism contributing to malign transformation and HCC development. We used the model of HepAD38 cell that contain the entire genome of HBV and where the virus replicates under control of a tetracycline-regulated promotor. We determined in these cells parameters of oxidative stress (malondialdehyde (MDA), glutathione (GSHtot) and oxidized glutathione (GSSG)) and the rate of cell growth. Karyotyping was performed on cells at the start of the experiment and at passage 6 and 18 of cells with no virus production or cells that produced HBV. Twenty-four hours after induction of HBV replication MDA and GSHtot had increased but returned to starting levels between 72 and 96 hours (both for HBV producing and non-producing cells). Cell growth was not affected during the first 6 days. However, the redox state of the cells (ratio GSSG/GSHtot) for cells that produced HBV was temporarily but significantly increased during the first four days with a peak at 72 hours. At 72 hours, using gene array, we could demonstrate a marked up-regulation of several genes involved in oxidative or metabolic stress (in particular SOD1, SOD2, GSR, MT1A) and a of heat shock proteins. Changes of the redox status have been linked to an influx of reactive oxygen species that can damage DNA. Karyotyping of HepAD38 cells (with or without HBV production) at different passages showed that virus production did not accelerate the accumulation of genetic changes. Although the virus production by HepAD38 cells is much higher than seen in HepG2.2.15 cells, we could not confirm previous observations that HBV production induces genetic changes and the mutations we observed should most likely be attributed to random genetic drift or selection. We conclude that HBV replication changes the redox state of the host cell but that HepAD38 cells can compensate for this stress after 4 days. We believe that HepAD38 cells can be a valuable tool to study liver cell responses on HBV replication but only during a limited experimental period (0-96 hours after induction).

- A 08 -

IMMUNOHISTOCHEMICAL STUDY OF THE EXPRESSION OF SOMATOSTATIN RECEPTORS IN SPLANCHNIC BLOOD VESSELS IN NORMAL AND IN CIRRHOTIC RATS. H. Reynaert (1), N. Uyama (1), Y. Jia (1), N. Chatterjee (2), D. Urbain (3), A. Geerts (1). (1) Laboratory for Molecular Liver Cell Biology, Vrije Universiteit Brussel (VUB) ; (2) Centre of Excellence, UCB, Brussels ; (3) Department of Gastroenterology-Hepatology University Hospital, Vrije Universiteit Brussel (AZ-VUB).

Background : Somatostatin has been used for over 2 decades to treat acute variceal bleeding. Although it has been assumed that one of the principal effects of somatostatin on lowering portal pressure is constriction of the splanchnic arteries, almost nothing is known about the expression of somatostatin receptors (SSTRs) in the splanchnic vessels.
Aim : This study was to investigate SSTR expression in splanchnic blood vessels of normal and portal hypertensive rats.
Methods : Cirrhosis was induced in 16 male Wistar rats by intra-peritoneal injection of 50 mg thioacetamide (TAA) twice a week for 14 weeks. Eight normal rats were used as control. Portal vein, superior mesenteric artery (SMA) and aorta were isolated and removed, and were immediately frozen in liquid nitrogen until use. Immunohistochemistry was performed using well validated and specific antibodies to SSTR subtypes 1-5. Approval of the institutes' ethical committee for animal care was obtained to perform this study.
Results : Microscopic examination of the liver confirmed that all rats treated with TAA had cirrhosis. Expression of SSTRs in different blood vessels is presented in table 1.
Conclusions : All 5 SSTRs are expressed by aorta, SMA, and portal vein, both in normal and cirrhotic rats. Whether the receptors are differently expressed in normal as compared to cirrhotic rats remains to be determined. Different expression may explain different hemodynamic effects of somatostatin in normal and cirrhotic animals.

	Aorta				**SMA**				**Portal Vein**			
	Normal		**Cirrhotic**		**Normal**		**Cirrhotic**		**Normal**		**Cirrhotic**	
	E	S	E	S	E	S	E	S	E	S	E	S
SSTR1	+	±	+	+	+	+	+	+	±	+	+	++
SSTR2	+	±	+	+	+	+	±	+	±	+	+	++
SSTR3	+	+	+	+	±	+	±	±	±	+	±	+
SSTR4	+	+	-	+	+	+	±	+	±	++	+	++
SSTR5	+/-	+	±	+	±	±	±	+	-	±	-	+

E : endothelial cells ; S : smooth muscle cells in tunica media.

- A 09 -

MESENTERIC ARTERY HYPOREACTIVITY OF CIRRHOTIC RATS IS NOT RESTORED AFTER ACUTE ADMINISTRATION OF OCTREOTIDE OR SOMATOSTATIN. I. Colle (1), A.M. Geerts (1), E. Vanheule (1), H. Van Vlierberghe (1), A. De Vriese (2), N. Lameire (3), J. Van De Voorde (3), M. De Vos (1). (1) Dept of Hepatology and Gastroenterology, (2) Dept of Nephrology, (3) Dept of Physiology, Ghent University Hospital.

Background : Cirrhosis is complicated by a splanchnic vasodilation and hyporeactivity towards vasodilators and vasoconstrictors. Octreotide and somatostatin may influence these hemodynamic disturbances. Previous experiments showed that early administration (at time of cirrhosis induction) of octreotide LAR could reverse this vascular hyporeactivity.
Aim : The *in vivo* response of mesenteric arteries to different vasoactive agents is studied in experimental animals with cirrhosis, treated with acute administration of octreotide, somatostatin or placebo.
Methods : Secondary biliary cirrhosis is induced in male Wistar rats by common bile duct ligation (CBDL, n = 23) and a second group is sham-operated (sham, n = 23). Four weeks after surgery, hemodynamics and mesenteric blood flow (MBF) are measured during infusion of the endothelium-dependent vasodilator acetylcholine (ACh), the NO donor detaNONOate, the potassium channel opener pinacidil and the vasoconstrictor phenylephrine directly in the mesenteric artery. The measurements are repeated after bolus and continuous infusion of octreotide ($CBDL_{octreo}$, n = 8 ; $sham_{octreo}$, n = 8) or somatostatin ($CBDL_{somato}$, n = 7 ; $sham_{somato}$, n = 7) or placebo ($CBDL_{plac}$, n = 8 ; $sham_{plac}$, n = 8).
Results : Baseline mean arterial pressure (MAP) is significantly higher and MBF lower in sham rats compared to the CBDL rats. Acute administration of both octreotide and somatostatin caused a significant decrease in MBF (-16 %+/-13 %, $p = 0.008$; and -16 %+/-11 %, $p = 0.01$, respectively) in CBDL but not in sham, comparable to MBF in sham animals. The *in vivo* MBF response to ACh, detaNONOate, pinacidil and phenylephrine is significantly lower in CBDL than in sham groups, suggesting hyporeactivity. The vascular hyporeactivity in CBDL rats is not corrected by the acute administration of octreotide or somatostatin.
Conclusion : This *in vivo* study confirms an impaired response to endothelium-dependent and -independent vasodilators and vasoconstrictor in the mesenteric artery of experimental animals with cirrhosis. This hyporeactivity is not restored by the acute administration of octreotide or somatostatin, while chronic administration of octreotide, shown in a previous study, could reverse this vascular hyporeactivity. However, octreotide and somatostatin cause a similar decrease (-16 %) in MBF in CBDL rats to values comparable as in sham animals, thus diminishing splanchnic vasodilation.

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INFLUENCE OF PEGINTERFERON-ALPHA THERAPY ON THE DECREASED LEUKOCYTE RECRUITMENT IN THE PERITONEAL MICROCIRCULATION OF RATS WITH PORTAL HYPERTENSION (PHT) AND CIRRHOSIS. A.M. Geerts (1), I. Colle (1), H. Van Vlierberghe (1), A. De Vriese (2), E. Vanheule (1), S. Mortier (2), N. Lameire (2), M. De Vos (1). (1) Department of Hepatology and Gastroenterology, (2) Department of Nephrology, Ghent University Hospital, Belgium.

Background & Aim : Patients with liver cirrhosis and PHT are predisposed to develop bacterial infections. We showed significantly impairment of leukocyte recruitment in peritoneal microcirculation of rats with PHT and cirrhosis. Leukocyte recruitment, a multistep process, is initiated by the selectin family of adhesion molecules. A role for soluble circulating L-selectin in inhibiting further leukocyte recruitment has been suggested. Interferon (IFN)-alpha-2a is the only cytokine reported to increase cell-surface density of L-selectin. The aim is to evaluate effect of pegIFN-alpha-2a therapy on impaired leukocyte recruitment.
Methods : Microcirculation of visceral peritoneum was visualized by intravital microscopy in Sham (n = 8), partial portal vein ligation (PPVL) (n = 8) and common bile duct ligated rats (CBDL) (n = 8), placebo or pegIFN treated. Peg-IFN was injected subcutaneously (18 µg, once a week).
Results : Baseline leukocyte rolling, adhesion and extravasation was not significantly different in Sham, PPVL and CBDL rats. In Sham rats, placebo and peg-IFN treated, infusion of LPS resulted in a significant increase in the number of rolling, adhering and extravasated leukocytes ($P < 0.005$). There is no difference in leukocyte recruitment between the placebo and peg-IFN treated group in Sham rats. In PPVL and CBDL rats, both placebo treated, there was only a minor increase in leukocyte rolling, adhering and extravasation over time and this was significantly lower than in Sham rats. Peg-IFN treatment in PPVL and CBDL rats resulted in a significant increase in the number of rolling leukocytes, comparable to levels as in Sham. There is no influence of peg-IFN on the number of adhering and extravasated leukocytes.
Conclusion : Leukocyte recruitment in response to LPS is significantly impaired in peritoneal microcirculation of rats with PHT and cirrhosis. Peginterferon-alpha treatment improves number of rolling leukocytes, but has no influence on adhesion and extravasation. Therefore, we can conclude several other mechanisms may be responsible for impaired leukocyte recruitment in PHT and cirrhosis.

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EPIDEMIOLOGICAL PROFILE OF 130 PATIENTS INFECTED WITH HEPATITIS C VIRUS GENOTYPE 4 IN BELGIUM. M. Nkuize (1), J.P Mulkay (1), N. Bourgeois (2), V. Muls (1), K. Kabeya (3), B. Caucheteur (1), R. Ntounda (1), A. Sarafidis (1), M. Buset (1), M. Adler (3). (1) Clinic of Hepato-gastroenterology CHU Saint Pierre, ULB Brussels ; (2) Department of Hepato-gastroenterology Hôpital Erasme, ULB Brussels ; (3) Clinic of Infectious Disease CHU Saint Pierre, ULB Brussels.

Background and Aim : It is well established that HCV genotype 4(HCV4) is the most prevalent variant of hepatitis C virus in Central Africa, Middle East and Egypt. Little have been published about HCV4 in Western countries and in Belgium in particular.
Methods : A retrospective multicenter review of all patient with HCV4 at CHU Saint Pierre and Hôpital Erasme, Brussels from March 2002 till March 2004. Parameters studies were : ethnic origin, age at diagnosis, gender, contamination risk factors, body mass index, viral load, and genotype and subtype, co-infection, transaminases (ALT), METAVIR classification and degree of steatosis. A total of 130 patients were identified. 6 patient were excluded because incomplete data. 92 patients underwent liver biopsy.
Results : The population were 83 African (A), 24 European (E), 17 Arab (Ar). According to ethnic origin we observed a significant difference for gender (A 39 % male, E 50 % male, Ar 76 % male, $p = 0.01$), mean age at diagnosis (A 48,17 years, E 34,16, Ar 40,70, $p < 0.0001$), body mass index (A 27,37, E 22,80, Ar 24,51, $p = 0,0004$), risk factors (A 51 % unknown, E 67 % IV drug user, Ar 35 % unknown, 35 % iv drug user, $P < 0,0001$), activity stage $\geq$ A2 (A 55 %, E 12 %, Ar 38%, $p = 0,006$). For viral subtype there were ethnic significant difference ($p < 0009$) : we have 6 subtype in African in comparison with only 3 subtype in Ar and 2 subtype in E mostly 4c/4d. There were no significant ethnic difference concerning viral load, fibrosis stage, degree of steatosis, abnormalALT. 19 patientshave co-infection in whom 17 with HIV(A 52 %, E 29,41 %, Ar 17,64 %), 2 with HBV (A 50 %, Ar 50 %).
Conlusion : **1)** The majority of patient emigrated from Central Africa, are female, have less overweigth and more acute activity.**2)**The diagnosis was made 18 years later in African **3)**The principal risk factor is unknown in African and Arab and iv drug user in Europeans. **4)** There were no difference regarding low viral load, abnormal ALT, degree of steatosis and fibrosis stage.

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PATIENTS INFECTED WITH HCV-5 PRESENT THE SAME RESPONSE RATE THAN PATIENTS INFECTED WITH HCV-1 : RESULTS FROM THE BELGIAN RANDOMISED TRIAL FOR NAIVE AND RELAPSERS (BERNAR-1). C. George (1), F. D'heygere (1), F. Nevens (3), H. Van Vlierberghe (4), O. Van Der Meeren (5). (1) AZ Groeninge, Kortrijk ; (3) UZ Gasthuisberg, Leuven ; (4) UZ Gent, Ghent ; (5)NV Roche SA, Brussels.

Introduction : HCV genotype 5 (HCV-5) shows a world-wide distribution mainly restricted to South Africa. However, a cluster of at least 80 patients has been detected in Belgium. The response rate of patients infected with HCV-5 has been poorly documented to date, but it has been suggested that HCV-5 could respond better to therapy than HCV-1.
Method : We reviewed the HCV-5 patients from the database of the Belgian Randomised Trial for Naïve and Relapsers (BERNAR-1), which has enrolled 443 patients that were naïve to therapy or relapsed after a conventional interferon (IFN) based therapy. Patients received either peginterferon alfa-2a (40KD) (PEGASYS) 180µg qw for 48 weeks (n = 11), either IFN 6 MIU tiw for 12 weeks then 3MIU tiw for 36 weeks (n = 10), both in combination with ribavirin 1000-1200mg/day for 48 weeks. A subset of HCV-1 infected patients was then selected from the study database to match the HCV-5 population according to age category (< vs > 40), gender (male vs female), baseline viral load category (< vs > = 800,000IU/mL), cirrhosis status (yes vs no), pretreatment status (naïve versus relapse) and treatment group (PEGASYS vs IFN).
Results : 21 patients with HCV-5 infection, and 21 patients with HCV-1 infection fully matching the characteristics of the HCV-5 patients, were identified in our database. In both groups, patients were mostly female (52 %), naïve to therapy (81 %), aged > 40 (95 %), had baseline viral load < 800,000IU/mL (62 %) and no cirrhosis (80 %). A sustained virological response (SVR) was observed in 10/21 patients in the HCV-5 group (48%) and in 8/21 patients in the HCV-1 group (38% ; $p = 0.530$) ; in the PEGASYS group, the SVR rate was 55 % in both HCV-5 and HCV-1 patients.
Conclusions : Patients infected with HCV-5 present the same response rate as patients infected with HCV-1. When treated with peginterferon alfa-2a (40KD) plus ribavirin for 48 weeks, 55 % of patients achieved an SVR.

HEPATIC STELLATE CELLS PROBABLY DO NOT DERIVE FROM THE NEURAL CREST. D. Cassiman (1), A. Barlow (2), L. Libbrecht (3), S. Vander Borght (3), J. Fevery (1), V. Pachnis (2). (1) Hepatologie, UZ Gasthuisberg, Leuven ; (2) NIMR, Mill Hill, London, UK ; (3) Pathologie, UZ Gasthuisberg, Leuven.

Background/Aim : Hepatic stellate cells (HSC) have been hypothesised to derive from the neural crest, based on their expression of multiple neural/neuroendocrine features and their contact with autonomic nerve endings. A transgenic mouse, expressing LacZ under control of a Wnt1 promotor/enhancer construct, previously showed faithful but temporary LacZ expression in all neural crest descendants (Echelard Y. *et al*. Development 1994 ;120 :2213-24). We used transgenic mouse technology to study the liver during embryonic development, to confirm or refute the hypothetical neural crest origin of HSC, as opposed to their equally hypothetical descendance from the septum transversum mesenchyme.
Methods : We studied a novel mouse line, established by inter-crossing mice expressing CRE recombinase under the control of a Wnt1 promotor/enhancer construct (see above), with a Rosa26 reporter line, expressing yellow fluorescent protein (YFP) preceded by a floxed STOP-cassette. In double transgenic mice, all cells expressing Wnt1 also start expressing CRE recombinase, which excises the STOP-cassette. This event leads to expression of YFP in these cells and all their descendants. Cellular YFP expression in these mice was studied and compared with desmin expression in wholemount embryo and organ preparations and paraffin sections, between embryonic day E11.5 and postnatal day P1.
Results : YFP was abundantly expressed in the central, the peripheral and the autonomic nervous system, in the whole neural crest and in all known neural crest-derived structures and cells (branchial arches, cardiac outflow tract, enteric nervous system, adrenal medulla, skin melanocytes). In particular, YFP expressing cells perfectly mimicked the time course and pattern of development of the enteric nervous system from neural crest cells migrating from the postotic region (vagal neural crest). Analysis of the liver showed that desmin-expressing, stellate-shaped, perisinusoidally located HSC were evident from E13.5 onwards, as expected. However, no detectable YFP expression was seen in the developing liver or in HSC, from E11.5 up until P1.
Conclusion : these findings suggest HSC do not descend from the neural crest, and therefore may derive from the septum transversum mesenchyme.

THERAPEUTIC EFFECT OF SOMATOSTATIN IN SCHISTOSOMA MANSONI CAUSED LIVER FIBROSIS. S. Chatterjee (1), G. Vrolix (1), M. Segers (2), I. Depoortere (3), T. Peeters (4), E. Van Marck (1). (1) Pathology Lab. Faculty of Medicine, University of Antwerp ; (2) UCB Pharma, Brussels, Belgium ; (3) GI Hormone Lab. Leuven.

The neuropeptide somatostatin is one of the major regulatory peptides in the central nervous system and the digestive tract. Our recent work has delineated an association between fibrosis and low levels of endogenous somatostatin plasma levels in Schistosoma mansoni infected subjects (Chatterjee *et al*. Acta Tropica 2004). Based on these results we explored the therapeutic potential of somatostatin in a mouse model of hepatic fibrosis associated with S. mansoni infections. Groups of outbred Swiss mice were infected with 100 S. mansoni cercariae, infection maintained till weeks 10 and 14, and then somatostatin (somatostatin-ucb®, UCB Pharma, Brussels) therapy delivered in two regimens — Either a one-day treatment (90µg per animal administered in 2 IV and 1 IP doses) or a two-day treatment (180µg per animal given in 6 doses). Infected animals that were untreated, uninfected age matched mice that also received somatostatin were included as controls. All animals were sacrificed one week after therapy and controlled for liver, spleen and total body weight. Livers were snap frozen in liquid nitrogen, fragments embedded in Tissue-tek OCT compound and 4µm thick sections were stained with haematoxylin-eosin or Masson's trichrome to study parasite count, hepatocyte status, granuloma size and cellularity. Fibrosis was assessed from the spectrophotometric determination of tissue hydroxyproline (Bergman & Loxley, 1963). Circulating somatostatin levels in the plasma of experimental and control mice were measured at the time of sacrifice by means of a radio-immuno assay. GraphPad Prism® was used for statistical calculations. Somatostatin administration showed little toxicity, probably due to its short half-life. Administration of 25µg resulted in circulating levels of 30233pg/ml (upon IP administration) and 17413pg/ml (upon IV administration) after 10 minutes. Total liver and spleen weights of S. mansoni infected animals increased over time, with no changes observed due to somatostatin therapy. Total body weights were decreased after infection but were not affected by somatostatin therapy. After somatostatin treatment mean egg counts per liver section (43.76 ± 3.56) were significantly reduced as compared to the egg counts in untreated mice after 10 weeks of infection (56.01 ± 3.34) ($p = 0.03$). Similar significant reduction in parasite egg counts were also observed after somatostatin treatment at 14 weeks of infection (56.62 ± 3.02) as compared to untreated animals (69.82 ± 2.77)($p = 0.006$). Infection with S. mansoni caused increased hydroxyproline levels (9.37 ± 0.63µmol at wk10 ; 9.65 ± 0.96µmol at wk14) as compared to uninfected animals (1.06 ± 0.10µmol). This significant increase in collagen content ($p = 0.01$; 0.007 respectively) marks the fibrosis observed at these time points. Treatment with somatostatin resulted in a significant decrease in hydroxyproline levels both at wk10 (4.76 ± 0.58µmol) and at wk14 (5.8 ± 1.13µmol) ($p = 0.01$; 0.03 respectively). Endogenous somatostatin levels were increased at wk10 (297 ± 37.24pg/ml) and wk14 (206 ± 13.30pg/ml) of infection as compared to uninfected mice (119 ± 11.99pg/ml) ($p = 0.01$; 0.008 respectively). Circulating somatostatin levels in infected animals were not significantly affected by somatostatin treatment. Hepatocyte status remained unaltered and granulomas were not remarkably changed in size or cellularity. Our experiments reveal an antifibrotic effect of somatostatin in schistosomiasis. We have previously shown that the somatostatin receptors SSTR2 and SSTR3 are present on the parasite egg and worms. We therefore hypothesize that somatostatin either destroys parasite eggs or reduces their secretion of fibrosis inducing mediators. Our data suggest somatostatin may have therapeutic potential in S.mansoni mediated liver pathology.

THE BASL REGISTRY OF NON ALCOHOLIC FATTY LIVER DISEASE (NAFLD). J. Henrion (1), S. De Maeght (2), M. Adler (3), S. Francque (4), P. Deltenre (5), C. de Galocsy (6), H. Orlent (7), W. Van Steenbergen (8), B. Bastens (9), E. Wain (10), P. Langlet (11), L. Lasser (12). (1) CH jolimont ; (2) CH Jolimont ; (3) Erasme, ULB ; (4) UZ, Antwerpen ; (5) CH Jolimont ; (6) HIS Bracops, Brussel ; (7) AZ St Jan, Brugge ; (8) Gasthuisberg, KUL ; (9) St Joseph, Liège ; (10) CH Verviers ; (11) Brugmann ; (12) Brugmann.

The demographic and metabolic characteristics of patients with NAFLD seen by hepatologists as well as the true prevalence of theMSand its components in these patients are not clearly established. Moreover the in the real life attitude of Belgian hepatologists regarding the indication of a liver biopsy and the induction of a treatment is unknown. The aim of this registry was to answer these questions.
Methods : BASL members were invited to collect cases of NAFLD seen from Jan 1 to Dec 31, 2004 and to fill a questionnaire including demographic, clinical, biochemical, investigational and therapeutic data.
Results (preliminary) : 158 patients were collected until mid November 2004. Mean age and gender were 48.3 y and 87M/71F, respectively. Mean BMI WAS 30.9 (± 4.5) kg/m^2 and only 6 patients had normal BMI. The prevalence of the MS (according to NHANES, ATP III) was 53 % and the mean MS score (according to the presence of the 5 components) was 2.6 ± 1.2. Among the 5 components of the MS, excessive abdominal perimeter was observed in 77 %, fasting glycemia e110 mg/dl or treated diabetes in 40.6 %, elevated triglycerides (TG) e 150 mg/dl in 56.5 %, low HDL cholesterol in 41 % and arterial hypertension in 45.7 %. Only 3 patients had none of the MS features. Fasting insulinemia e20 µu/ml was observed in 54.7 % and was more elevated in patients with MS (mean 27.02 ± 10.9) than in patients without (mean17.65 ± 6.09, p = 0.0004). Marked increase in ALAT levels (> 5 × ULN) was observed in only 1.2 % of the cases, but marked increase of ggt (> 5xULN) was observed in around 10 % of patients (15/152). Patients with ggt > 5xULN were significantly older (55.9 v 47.64, p = 002), had more often treated diabetes (53 % v 22.6 %, p = 0.01)and had more elevated TG (median : 215mg v 159, p = 0.003). A liver biopsy was performed in 37.5 % and a pharmacological treatment was introduced by the hepatologist in 26 %. Large variations were observed between practitioners regarding their practical attitude.
Conclusions : 1) The typical NAFLD patient seen by hepatologists is a middle aged man or woman with slight obesity and hypertriglyceridemia. 2) NAFLD is linked to the MS, but only 53 % of the patients had this syndrome according to international definition. 3) Patients with marked elevation of ggt have peculiarities and it could be interesting to test if these patients have more severe liver fibrosis. 4) The attitude of practitioners regarding liver biopsy and treatment largely differs, reflecting the lack of evidences in these matters.

NON ALCOHOLIC NON OBESITY TREATED FATTY LIVER DISEASE (NANOFLD) IS THE MAJOR CAUSE OF CHRONIC CRYPTOGENIC LIVER DISEASE. B. Vos, N. Nagy, F. Fery, M. Cnop, M. Adler. Hôpital Erasme, Brussels.

Chronic unexplained liver tests abnormalities remain a distinct clinical problem. Of the 1777 liver biopsies performed in our unit between November 1999 and October 2004 for the staging of various chronic liver disorders, cryptogenic liver disease, defined as the persistence of abnormal liver tests in the absence of excessive alcohol intake (> 40 g/day in male and > 20 g/day in female), obesity (BMI > 30 kg/m^2), diabetes (glycemia > 126 mg/dl or a random glycemia > 200 mg/dl), hepatotoxic drug use or positive diagnostic blood tests, was observed in 132 patients (7.4 %). Of these, normal liver histology was observed in 25 (19 %) and non alcoholic non obesity related liver disease (NANOFLD) in 50 (38%). Sufficient data were available in 32 patients (median BMI 26 kg/m^2, IQR 23-29) who were compared with 51 of the 131 initial patients with classical NAFLD confirmed by liver biopsy. Compared to the NAFLD group, patients with NANOFLD were younger : median age (IQR) : 40 (27-70) vs 50 (25-71), p = 0.04, more often male : 69 % vs 45 %, p = 0.03, had clinical features of the metabolic syndrome according to the ATPIII working group in 70 % and insulin resistance measured by the HOMA-IR test in a similar proportion : median (IQR) : 2.25 (1.01-7) vs 4.31 (2.04-16.4), p = 0.11. Liver histology, according to Brunt's classification revealed lesser (p = 0.04) significant (^{3} S2) fibrosis in the NANOFLD group. This study reveals that NANOFLD is responsible for 38% of the causes of cryptogenic liver disease, which in itself represents 7 % of the indications of liver biopsy. NANOFLD being associated with insulin resistance and features of the metabolic syndrome might represent an early predictor of metabolic disorders and these patients should probably enter a surveillance program.

INDUCTION OF SEVERE INSULIN RESISTANCE AND HEPATIC COMPLICATIONS COMPATIBLE WITH NASH IN MICE FED A WESTERN-TYPE DIET. C. Dewever, Y. Horsmans, I. Leclercq. Gastroenterology Unit, UCL.

Insulin resistance is a major factor implicated in the pathogenesis of nonalcoholic steatohepatitis (NASH).
Aim : To evaluate the effects of high-glucose and/or high-saturated fat/cholesterol diet on emergence of insulin resistance and liver pathology.
Methods : Male C57BL6/J mice were fed ad libitum for 5 weeks a standard chow (CT group, n = 4), a standard chow with high-glucose in drinking water (glucose group, n = 6) or a diet enriched in saturated fat and cholesterol together with high-glucose in drinking water (SFA group, n = 6). Intraperitoneal glucose tolerance and insulin resistance tests were performed in vivo. At the end of the experimental period, blood and tissue samples were obtained for analyses.
Results : Compared with CT, mice from glucose and SFA groups exhibited hyperglycemia (145 ± 5 and 177 ± 8 *versus* 124 ± 2 mg/dL, both $p < 0.001$) and hyperinsulinemia (25.8 ± 4.7 and 30.3 ± 1.6 *versus* 2.8 ± 0.1 ng/mL, both $p < 0.001$). As assessed *in vivo*, mice of glucose group and, to a greater extend, mice of SFA group had glucose intolerance ($p = 0.004$ and $p < 0.001$, respectively) and insulin resistance ($p = 0.007$ and $p = < 0.001$ respectively), which was confirmed by a significant ($p < 0.001$) rise in the HOMA-IR index (0.3 ± 0.1, 3.3 ± 0.6 and 4.7 ± 0.3 in CT, glucose and SFA, respectively). Liver histology appeared normal in mice from CT and glucose groups, but mice in SFA group developed significant macrovesicular steatosis, hepatocyte ballooning and apoptosis and variable panlobular inflammation. Consistently, intrahepatic lipids were significantly increased in SFA *versus* CT (9.0 ± 4.7 *versus* 1.8 ± 0.5 mg lipid/100 mg liver, $p = 0.02$). Importantly, steatohepatitis in SFA mice was associated with a significant up-regulation of collagen Ia1 mRNA expression (1.7 ± 0.4 *versus* 1.0 ± 0.2 in CT, $p = 0.01$).
Conclusions : A diet enriched in glucose, saturated fatty acids and cholesterol induced a severe and prolonged insulin resistance in mice. This was associated with hepatic damage, including activation of fibrogenesis, compatible with NASH. We believe that this original mouse model will be useful to analyse the role of insulin resistance and nutritional factors in the pathogenesis of NASH and for evaluation of treatment.

DETAILED AND UNIFORM PATHOLOGICAL EVALUATION OF CIRRHOTIC EXPLANT LIVERS REVEALS HEPATOCELLULAR CARCINOMAS WITH NUMEROUS SMALL INTRAHEPATIC METASTASES AND GIVES NEW INSIGHTS INTO TUMOR PROGRESSION. L. Libbrecht (1), D. Cassiman (2), C. Verslype (2), T. Roskams (1). (1) Department of Pathology, (2) Department of Hepatology, University Hospitals Leuven.

Most studies on hepatocellular carcinoma (HCC) in explant livers apply a broad liver sectioning with variable slice thickness. Consequently, some HCCs remain undetected and pathological staging is inaccurate, biasing conclusions of these studies. We recently proposed golden standard pathological evaluation of explants.
This method includes uniform liver slicing at 5-mm intervals with biopsies of each macroscopical lesion followed by microscopical classification. This golden standard method was applied on 108 cirrhotic explant livers. When possible, HCCs were classified as primary or intrahepatic metastasis (IM) according to WHO-guidelines. Predominant differentiation and microvascular invasion was noted. One or more HCCs were present in 32 patients (30 %). Three livers in which presumed HCC(s) were completely destroyed by pretransplant treatment and 2 livers in which not all HCCs could be confidently classified as primary or IM were excluded. 11 of the remaining 27 patients (40 %) had at least one IM ; the mean diameter of IMs was 4.3 mm (range 2-10). Six patients (22 %) had a HCC with at least 3 IMs (maximum : 27 IMs) and thus exceeded UNOS-criteria. Due to their small size, IMs were rarely detected during pretransplant imaging ; only the primary, larger HCC was detected. Two patients with multiple IMs in their explant liver died of HCC recurrence during mean follow-up of 17 months. IMs were only seen in HCCs larger than 20 mm. An increase in diameter of primary HCC was associated with an increase in IM number, a poorer differentiation and frequent microvascular invasion ($p < 0.0005$). Six primary HCCs were outliers from this pathway : 3 were large (> 5cm), but were still well differentiated and showed neither microvascular invasion nor IMs. Conversely, 3 HCCs showed prominent microvascular invasion and had much more IMs (between 9 and 27) than expected according to their diameter (between 35 and 60 mm).
In conclusion, patients with numerous small IMs in their explant liver can only be recognized by the ‘golden standard’ pathological evaluation. There is a general HCC progression pathway in which increase in diameter is closely linked with decreased differentiation and increased IM number. Some HCCs deviate from this pathway and are either metastasis-resistant or metastasis-prone.

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AN EXPERIMENTAL MODEL OF MICRONODULAR CIRRHOSIS INDUCED BY SUBCUTANEOUS ADMINISTRATION OF CARBON TETRACHLORIDE IN MICE. E. Vanheule, A.M. Geerts, H. Van Vlierberghe, M. De Vos, I. Colle. Department of Hepatology and Gastroenterology. Ghent University Hospital. Belgium.

Objectives : Carbon tetrachloride (CCl4) is a strong hepatotoxin. Acute CCl4 administration results in acute hepatocellular injury. Chronic administration leads to repeated tissue injury, which stimulates both hepatocyte regeneration and active fibrogenesis resulting in a distortion of the liver architecture that finally leads to cirrhosis. The time required to develop cirrhosis varies from animal to animal. Most models are induced by intraperitoneal injection, however, as we want to examine the peritoneum and liver by intravital microscopy, peritoneal injection may cause damage and sticking of peritoneum and bowel.
Aim : To develop an experimental animal model of micronodular cirrhosis in mice using CCl4 *subcutaneously*.
Methods : In male Swiss mice (n = 15) (20-25g) cirrhosis was induced by dorsal subcutaneous (SC) injection of CCl4 (1:1 in olive oil ; 1 mg/kg) twice weekly. Control mice received pure olive oil (1 mg/kg) SC. Mice were sacrificed after 8, 10 and 12 weeks of CCl4 treatment to evaluate the development of fibrosis/cirrhosis by the Metavir score. Fragments of each liver lobe were processed for histological examination (Haematoxylin-eosin and Sirius Red staining). The portal venous pressure (PVP) was measured by placing a catheter in the ileocolic vein.
Results : After 8 weeks, mice developed fibrosis, scored as F2-F3 on histological examination. After 10 weeks, mice developed F3 fibrosis but no cirrhosis. After 12 weeks, almost all mice developed micronodular cirrhosis, scored as F3-F4 on histological examination. The cirrhosis is uniform in the whole liver. The PVP was significantly higher in CCL4 mice (10.6mmHg) vs control mice (5mmHg) ($p = 0.008$). The mice didn't develop ascites at this time point. There was no sticking of the peritoneum and bowel.
Conclusion : After 12 weeks of *subcutaneous* injection of CCl4 (1:1 in olive oil ; 1 mg/kg) twice weekly, mice develop liver cirrhosis and portal hypertension, but they do not develop ascites at this time point. This mice model can be used as a model for micronodular cirrhosis, without lesions in peritoneum, sticking of the liver and bowel. This model is convenient for intravital microscopy of the liver. Further administration of CCl4 after 12 weeks can perhaps lead to ascites formation, which is now in development.

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EUROPEAN NETWORK FOR VASCULAR LIVER DISORDERS "EN-VIE" : PROSPECTIVE DATA DURING THE FIRST YEAR. P. Langlet (1), L. Lasser (2), J. Martinet (3), P. Gruselle (4), M. Adler (5), S. Murad Darwish (6), H. Janssen (6), J. Delwaide (6), J. Garcia-Pagan (8), E. Elias (9), M. Primignani (10), D. Valla (11). (1) CHIREC and CHU Brugmann, ULB ; (2) CHU Brugmann, VUB-ULB ; (3) Clinique Mont-Godinne, UCL ; (4) CHU Vésale, ULB ; (5) Hôpital Erasme, ULB ; (6) Erasmus Hospital, Rotterdam, NL, CHU Sart Tilman ; (8) Hospital Clinic I Provincial de Barcelona,SP ; (9) Queen Elisabeth Hospital, Birmingham,UK ; (10) IRCSS Ospedale Maggiore di Milano, Ita ; (11) Hôpital Beaujon, Paris, France.

Introduction : Vascular diseases of the liver represent a heterogeneous group of rare disorders usually affecting young subjects and associated with a poor spontaneous outcome. Hepatic vein thrombosis "Budd-chiari syndrome" (BCS) and non tumoral and non cirrhoric acute portal vein thrombosis (PVT) remain under-recognized and poorly understood disorders. Treatments of these disorders (anticoagulation, surgery,...) have been empirically developped and poorly assessed. Because limitations associated with retrospective studies, we started1october 2003, a prospective European study(with European Comunityfunding) to collectall cases of BCS and PVT during at least 2 years in 10 european countries.
Aims : To collect high quality data for clinical studies in a large cohort of patients investigated and managed in the most appropriate possible manner. To merge these data into a large European data base to analyses on cause, prognosis and assessement of therapy. To collect and register well characterised samples for clinical and basic investigations in national level and in Europe.
Methods : Since 1 october 2003, all > 16 years old patients with newly diagnosed BCS or PVTwithout tumoral causehad to be notified to EN-Vie investigator in a national level. After informed consent, registration was performed and baseline and follow-up data were completed in an European electronic Case report form. Results from available European and Belgium data are shown below. More complete data will be presented in February.
Results : 147 patients (74BCS and 73 PVT) are registered in the study in1 year with81 % BCS and 84 % PVT eligible. In Belgium, 5 BCS (national level) and 3 acute PVT (only in the investigator center) were included. For BCS : median age = 45.9 years with 76 % female. Duration of disease before diagnosis was < 1 month in 42 % ; 1-6 month in 42 % and > 6 months in 16 %. The majority of patients had Child-Pugh B (62 %) whereas 23 % had Child-Pugh C. In 16/25 pts hypercoagulable aetiology was found. For PVT : median age = 43,5 years with 56 % female. Duration of disease before diagnosis was < 1 month in 83 %. Hypercoagulable aetiology was found in 50 % of cases. The majority of patients had no liver insuffisiency (Child-Pugh A = 62 %) and anticoagulation was given in 66 % of PVT.
Conclusions : Vascular liver disorders are very rare. Prospective studies are required to collect a large number of patients followed-up for a long period of time. Underlying causal factors are likely to have a great impact on the outcome. Adjustement on prognostic variables in a large cohort will be neccessary.

NON SPECIFIC CHOLESTATIC SYNDROM AFTER LIVER TRANSPLANTATION. PROGNOSIS AND RISK FACTORS. A. De Roover (1), N. Meurisse (1), T. Marival (1), O. Detry (1), J. Delwaide (2), M. Meurisse (1), P. Honoré (1). (1) Service de Chirurgie Abdominale et Transplantation, (5) Service d'Hépato-Gastroentérologie, CHU, Liège.

Introduction : Cholestasis after liver transplantation is common. Differential diagnosis includes vascular thrombosis, biliary obstruction, rejection, medication effect or sepsis. When these factors have been excluded, one is left with a non specific cholestatic syndrome whose etiology and prognosis remain ill-defined.
Material and Methods : We retrospectively reviewed the charts from 142 consecutive patients transplanted with a liver in our institution from 1998 to 2000. A cholestatic syndrome (defined as non-normalization or reelevation of bilirubin and gGT) was identified in 69 patients in the immediate postoperative period, and was evaluated with US, ERCP, MRI, percutaneous cholangiography or biopsy. In 44 patients (69 %) a causative factor was identified (hepatic artery thrombosis (n = 7), isolated biliary anastomotic stricture (n = 10), rejection (n = 21), HCV recurrence (n = 3), CMV infection (n = 1), tumor (n = 1) and PNF (n = 1). The clinical and biological course of the 25 remaining patients was studied to identify the prognosis of this cholestatic syndrome. We then compared, in a multivariate analysis, parameters from the donor, the recipient, the procurement and the perioperative period to those from 25 random patients transplanted during the same period, who had an uneventful liver recovery after transplantation.
Results : Twenty-five had an early peak of cholestasis after a mean of 6 days. The early workup showed in one case a picture of diffuse intrahepatic biliary strictures and in 9 cases preservation injury at biopsy. Twenty of the 25 patients (80 %) presented a second late peak of cholestasis (mean 6 months). At that time, diffuse alteration of the intrahepatic bile ducts was shown in 14 patients associated in 8 cases with a main bile duct stenosis. Clinical course was variable with a clinical and biological return to normal in 6 patients. Six patients died. Nine patients had a biliary procedure (choledocojejunostomy, dilatation or stent placement). Multivariate analysis showed length of liver procurement procedure and presence of a liver vascular anomaly as significant factors between the study group and the control group.
Conclusion : This non specific cholestatic syndrome was associated in our series with significant morbidity and mortality. It was associated with a spectrum of lesions, of which the diffuse intrahepatic type characterized the full blown syndrome.Prevention of this syndrom should begin with avoidance of prolongedischemia of the graft

INFLUENCE OF BODY MASS INDEX (BMI) ON THE RESULTS OF DIFFERENT INTERFERON-BASED REGI MENS FOR THE TREATMENT OF CHRONIC HEPATITIS C. H. Aktas, S. Francque, S. Vogels, E. Van den Bogaert, P.A. Pelckmans, P.P. Michielsen. Gastroenterology and Hepatology,University Hospital Antwerp (UZA), Edegem, Belgium.

Introduction : Although the efficacy of antiviral therapy in chronic hepatitis C has improved since standard interferon (IFN) monotherapy was introduced, nonresponse to the current therapies remains common. Several predictive factors have been shown to influence response. Obesity, a modifiable risk factor, may have a negative effect on treatment response to both pegylated and standard IFN monotherapy.
Aims : 1) To describe the characteristics of hepatitis C patients 2) To compare the efficacy of different treatment modalities 3) To identify the independent factors, which influence the sustained virologic response.
Patients and methods : A retrospective review was performed of all patients with chronic hepatitis C at our centre from 1990 to 2004.
Results : Of the 229 patients 133 (58%) were male, with a mean age at diagnosis of 44.0 ± 14.2 y. Genotype (G) distribution was as follows : 58.1 % G 1, 7.2 % G 2, 25.7 % G 3, 7.8% G 4 and 1.3 % G 5. Blood transfusion (30 %) and IV drug use (30 %) were the most important modes of transmission. 152 patients were treated with 242 therapy courses, with complete data for 191 treatments. Sustained virological respons (SVR) rates were 10.4 %, 30.0 %, 24.0 % and 42.1 % for IFN monotherapy, IFN-ribavirin combination therapy, Peg-IFN ± 2b-ribavirin and Peg-IFN ± 2a-ribavirin combination therapy respectively. SVR was significantly better for G 2 and 3 compared to G 1 and 4 ($p = 0.011$). Ethnic origin was also of influence ($p = 0.043$) with a worse SVR in the black race (mainly G 4). Strikingly, BMI - defined as 3 categories- normal : < 25 kg/m^2, overweight : 25-30 kg/m^2, obesity : > 30 kg/m^2- was a highly significant predictor of SVR ($p = 0.002$) with overall SVR of 37.3 %. 13.6 % and 11.1 % respectively.
Conclusion : The results of the different treatment regimens for chronic hepatitis C at our centre reflect the current experience, with a superior result for the IFN-ribavirin combination therapy. Besides G 1 and black race, a higher BMI is strongly associated with a lower SVR even in the weight-based treatment regimens. As overweight is increasingly common, this factor should be taken into account in tailoring hepatitis C treatment.

TREATMENT OF CHRONIC HEPATITIS C IN PATIENTS CO-INFECTED WITH HIV WITH WEEKLY PEGINTERFERON AND RIBAVIRIN. P. Michielsen (1), E. Bottieau (2), H. Van Vlierberghe (3), Belgian Association for the Study of the Liver. (1) Division of Gastroenterology, University Hospital Antwerp ; (2) Institute of Tropical Medicine, Antwerp ; (3) Division of Hepatogastroenterology, University Hospital Gent ; (4)NA.

Background Chronic hepatitis C represents a leading cause of morbidity and mortality among HIV-infected patients worldwide, whereas classic opportunistic complications have declined dramatically as a result of HAART. Recently, combination of peginterferon and ribavirin has become standard therapy for chronic hepatitis C. Data on treatment of HIV-HCV co-infected patients with this combination are limited. Therefore, the efficacy and safety of peginterferon alpha-2b and ribavirin in HIV-HCV co-infected patients was evaluated in Belgium.
Methods An open labeled multicentre study was started in Belgium in September 2001. Inclusion criteria were : naïve patients, HCV-RNA positive, elevated ALT, anti-HIV positive, CD4 cells > 200/µL, compensated liver disease, stable HIV disease with or without HAART. Eligible patients were treated with peginterferon alpha-2b (PegIntron®) 1.5 µg/kg/wk in combination with ribavirin (Rebetol®) 800-1200 mg qd according to the patient's weight for 52 weeks. Treatment was interrupted in case of virological nonresponse at week 24.
Results : Fourty patients were included between Sep 2001 and Dec 2003 (mean age 38 - range 17-61 years ; 69 % male, 83 % caucasian and 17 % negroid). Genotype 1 was present in 10/32 patients (31.3 %), 2 in 1/32 (3.1 %), 3 in 10/32 (31.3 %), mixed 2 and 3 in 1/32 (3.1 %) and 4 in 10/32 (31.3 %). Basal viral load was high (> 850,000 IU/mL) in 14/27 (52 %) of the patients. Mean CD4 count at baseline was 561/µL (range 14440-220). Twenty four of the patients were treated with HAART. Thirty four patients started treatment. Early withdrawal was noted in 20 patients : in 11 for side effects (7 SAE) and in 9 patients for virological nonresponse at week 24. Eight patients completed full treatment up to now. One of them was PCR positive at end of treatment. At week 24 of follow-up, in 5 a sustained virological response (SVR) was noted, in 1 a relapse, whereas in 1 the result is still pending. Of those with SVR, 3 were infected with genotypes 2 and/or 3, 2 with genotype 1b.
Conclusions : From these preliminary data it can be concluded that :

1. The distribution of genotypes is remarkably different from that in HCV mono-infected patients with relative over-representation of genotypes 3 and 4.
2. Treatment of HCV is associated with a high rate of early withdrawal due to side effects.
3. When treatment can be completed, SVR is possible, especially in genotypes 2 and/or 3.

HCV GENOTYPES 2 AND 3 : THE PREDOMINANT GENOTYPES AT THE HORIZON 2020 ? J. Delwaide (1), C. Gérard (2), D. Vaira (3), B. Bastens (4), B. Servais (5), E. Wain (6), C. Bataille (7), G. Daenen (8), O. Detry (9), A. DeRoover (10), P. Honoré (11), M. Meurisse (12), B. Rentier (13), J. Belaiche (14). (1) Gastroenterology CHU Sart Tilman ; (2) Immuno-Hematology CHU Sart Tilman ; (3)Immuno-Hematology CHU Sart Tilman ; (4) Gastroenterology St Joseph ; (5)Gastroenterology Bois Abbaye ; (6) Gastroenterology La Tourelle-Peltzer ; (7) Gastroenterology CHR Huy ; (8) Gastroenterology CHU Bruyères ; (9) Surgery CHU Sart Tilman ; (10) Surgery CHU Sart Tilman ; (11) Surgery CHU Sart Tilman ; (12) Surgery CHU Sart Tilman ; (13) Virology CHU Sart Tilman ; (14) Gastroenterology CHU Sart Tilman.

Currently, genotype 1b is largely the predominant genotype among HCV patients (pts). Distribution of genotypes, however, is changing with time, with a relative diminution of genotype 1b and 2 and an increase of genotypes 3a, 1a and 4.
AIM : To quantify mathematically this evolution and to predict the distribution of genotype in incidental cases in the future.
Method : In our data base, genotype and date of the first consultation were known for 1109 pts. The evolution with time of the relative distribution of each genotype year after year from 1992 to 2004 was calculated in incidental cases by using a linear regression model. The determination of the slopes allowed evaluating the evolution of genotype distribution for the future.
Results : Global distribution of genotypes was 62 % of genotype 1, 14 % of genotype 3, 12 % of genotype 2, 11 % of genotype 4, 1 % of genotypes 5, a distribution very similar to those observed in the bordering countries. The proportion of incidental cases infected with genotype 1b decreased linearly of about -2.03 % / year ($p < 0.0000001$). Incidence of genotype 1b in new cases could therefore tend to 0 around 2025. Genotype 1a increased slightly of +0.75 % / year ($p = 0.03$). Genotypes 2, 3, 4, 5 did not vary significantly with time during this period. The decreasing slope of genotype 1 (1a+1b) and stable slope of genotype 2 and 3 will intersect around 2020.
Conclusions : Provided the trends observed during the last decade are confirmed with time, we could anticipate that, in our population, the proportion of new cases with easy-to-treat genotypes (2 and 3) will overtake the proportion of new cases with difficult-to-treat genotypes (1a+1b) around 2020.

MODIFIED SUZUKI SCORE FOR HISTOLOGICAL SCORING OF 'PRE-NECROTIC' TISSUE DAMAGE IN THE EARLY REPERFUSION PHASE OF HEPATIC ISCHEMIA/REPERFUSION INJURY. B. Maesen (1), T. Chapelle (1), K. Van De Vijver (3), G. Behets (4), J. P. Bogers (3), M. De Broe (4), D. Ysebaert (1). (1) Department of Experimental Surgery, (3) Department of Pathology, (4) Department of Nephrology, University of Antwerp, Belgium.

Aim : Different histological scoring systems nowadays exist to score necrosis and/or fibrosis in the liver, but are only suitable for describing necrosis and/or fibrosis, except for the Suzuki Score. The classical Suzuki score was developed to score post-ischemic necrosis. We applied this Suzuki Score for scoring 'pre-necrotic' tissue damage very early (< 4 hours) after Ischemia/Reperfusion Injury (IRI), thereby comparing comparative microscopy (Classical Suzuki) with a more mathematical system (Modified Suzuki) to improve the objectivity of the score system.
Methods : IRI was performed in Lewis rats with partial liver clamping (45'). After reperfusion (1h, 2h, 4h), liver sections were stained with Haematoxyline-Eosine and investigated by light microscopy (10x40x). First, only established necrosis was measured and calculated as % necrotic area. Second, the Classical Suzuki Score was applied using 5 standard slides representing different grades of damage, with a score from 0 to 4 using a combination of changes in sinusoidal congestion, cytoplasmatic vacuolisation, and necrosis. Third, in a modified Suzuki Score, presence or absence (+/-) of each of the 3 Suzuki Criteria (congestion, vacuolisation and necrosis) was determined independently and applied on periportal and pericentral fields.
Results : 1. Vascular congestion and vacuolisation were both already present at 1h. 2. Necrosis became apparent only after 2h. 3. The classical Suzuki score did not allow to discriminate post-I/R damage between the different time points within the first 4 hours 3. In our modified Suzuki Score, vacuolisation (Microvesicular Steatosis (MVS))was significantly more present pericentral than periportal.
Conclusions : 1. The modified Suzuki Criteria Score allowed a more refined and mathematical score system, specific in the early reperfusion phase after hepatic IRI. 2. Damage of IRI seems to be more present in the pericentral area than in the periportal area. 3. Pericentral vacuolisation (MVS) is a more refined indicator for damage of very early IRI.

PEGINTERFERON ALFA-2A (40KD) PLUS RIBAVIRIN IS AS EFFECTIVE IN PATIENTS RELAPSING AFTER CONVENTIONAL INTERFERON BASED THERAPY THAN IN NAÏVE PATIENTS : RESULTS FROM THE BERNAR-1 TRIAL. F. Nevens (1), H. Van Vlierberghe (2), F. D'heygere (3), J. Delwaide (4), M. Adler (5), J. Henrion (6), J. Henry (7), A. Hendlisz (8), P. Michielsen (9), B. Bastens (10), R. Brenard (11), O. Van Der Meeren (12). (1) UZ Gasthuisberg, Leuven ; (2) UZ Gent, Ghent ; (3) AZ Groeninge, Kortrijk ; (4) CHU Liège, Liège ; (5) Cliniques universitaires Erasme, Brussels ; (6) Hôpital de Jolimont, La Louvière ; (7) CHU Charleroi, Charleroi ; (8) Institut Bordet, Brussels ; (9) UZ Antwerpen, Edegem ; (10) CH Saint-Joseph-Espérance, Liège ; (11) Hôpital Saint-Joseph, Gilly ; (12) NV Roche SA, Brussels.

Background : Treatment with peginterferon alfa plus ribavirin (RBV) is standard of care in the initial treatment of chronic hepatitis C (CHC). The Belgian Randomised trial for Naïve and Relapsers (BERNAR-1) investigated the safety and efficacy of this regimen versus a conventional interferon-based combination therapy, and compared naïve patients versus patients who relapsed after initial treatment with conventional interferon with or without ribavirin.
Methods : Study medication consisted of peginterferon alfa-2a (40KD) (PEGASYS) 180µg qw for 48 weeks, or interferon alfa-2a 6MIU tiw for 12 weeks then 3MIU tiw for 36 weeks (IFN), both combined with RBV (1,000 or 1,200mg/day) for 48 weeks. Randomisation was stratified according to pretreatment status (treatment-naïve versus relapse) and presence of cirrhosis.
Results : 443 patients were randomised and received at least one dose of study medication (ITT, missing = failure). The baseline parameters were well balanced across treatment arms. The patients were predominantly male (54 %), Caucasian (91 %), older than 40 (68%), with a BMI > 25kg/m^2 (50 %) ; 16 % had cirrhosis ; 22 % were relapsers. At baseline, 63 % of patients had genotype 1 infection and 34 % had HCV-RNA > 800,000IU/mL. A significantly higher proportion of patients in the PEGASYS group than in the IFN group had a sustained virological response (SVR) : 52 % vs. 27 %, $p < 0.001$. The proportion of patients with SVR in the naïve population was 54 % (PEGASYS) versus 27 % (IFN) ; in the relapse group, 43 % (PEGASYS) vs. 26 % (IFN). The difference between treatment groups was highly statistically significant in both naïve and relapse populations ($p < 0.001$), while the difference in response rate between naïve and relapsers was not statistically significant ($p = 0.237$).
Conclusions : The CHC population in Belgium shows various factors usually associated with lower response to therapy. Despite this, peginterferon alfa-2a (40KD) plus ribavirin demonstrates efficacy results of 54 % SVR that are consistent with previous reports. In patients relapsing after conventional interferon-based therapy, once-weekly peginterferon alfa-2a (40KD) plus ribavirin provides similar response rate than in naïve patients.

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TREATING BELGIAN NAIVE CHRONIC HEPATITIS C PATIENTS WITH PEGINTERFERON ALPHA2B ABD RIBAVIRIN IN REAL LIFE (THE PEGINTRUST STUDY). M. Adler (1), B. Bastens (2), I. Colle (3), J. Delwaide (4), J. Henrion (5), Y. Horsmans (6), P. Michielsen (7), J. Mulkay (8), P. Yap (9), H. Van Vlierberghe (10). (1) Hôpital Erasme, Brussels ; (2) Hôpital St Joseph, Liège ; (3) UZ Ghent, Ghent ; (4) CHU Liège, Liège ; (5) Hôpital Jolimont, La Louvière ; (6) UCL St Luc, Brussels ; (7) UZ Antwerpen, Antwerpen ; (8) CHU St Pierre, Brussels ; (9) KULeuven, Leuven ; (10) UZ Ghent, Ghent.

The applicability, in real life of the results of large international, randomised therapeutic trials of hepatitis C is not well known. In an independent observatory, 64 clinicians from 46 different Belgian general and academic hospitals, treated for 48 weeks, from January 2003 till October 2004, 241 patients with genotype 1, 4 and 5 and significant fibrosis with PEG-IFNa2b and ribavirin outside clinical trials : 55 % were male ; median age was 51 (IQR 22-78) ; weight was 74 kg (IQR : 45-120) ; median BMI 25 kg/m^2 (IQR 17-42) ; 23 % were intravenous drug users ; 83, 14, and 3 % had genotype 1, 4 and 5 ; 58, 22 and 20 % had stage 2, 3 and 4 fibrosis according to METAVIR and baseline viral load was above 800,000 IU/ml in 49 % of them. Within the first 12 weeks, therapy had to be discontinued before the planned term in 21 patients (8.7 %) : non compliance in 4, adverse effect in 11 and serious adverse effects in 6. Median time lag between starting and stopping treatment was 73 days (IQR 18-99). There was one death from sepsis and multiple organ failure. Of the 41 patients for whom complete virological data were available at week 12, early virological response (EVR) was observed in 95 (67 %). From these preliminary data, we can conclude that, compared to the Mann's trial and the Davis' analysis, Belgian patients treated in real life were leaner, older, had more significant fibrosis while achieving similar EVR and lower early treatment discontinuation rate.

1 Lancet 2001 ; 2 Hepatology 2003

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VALUE OF THE FIBROTEST FOR THE STAGING OF HEPATITIS C : AN EXTERNAL VALIDATION STUDY. M. Adler (1), P. Thiry (2), B. Frotscher (3), S. Evrard (4), T. Gustot (5), N. Nagy (6), P. Langlet (7), N. Bourgeois (8). (1) Hôpital Erasme, Brussels ; (2) Hôpital Erasme, Brussels ; (3) Hôpital Erasme, Brussels ; (4) Hôpital Erasme, Brussels ; (5) Hôpital Erasme, Brussels ; (6) Hôpital Erasme, Brussels ; (7) CHU Brugmann ; (8) Hôpital Erasme, Brussels.

There is an urgent need of reliable non-invasive markers of liver fibrosis, as an alternative to liver biopsy which has dis-advantages and drawbacks. The Fibrotest (FT) is one of them but has been validated externally only in one study with lower predictive values ([1]). Of the 133 FT values performed in our unit since June 2004, 17 (13 %) were outside the 99 percentiles : 4 with haptoglobin < 5 mg/dl, 4 with haptoglobin > 320 mg/dl, 3 with apo A1 > 250 mg/dl, 1 with apo A1 < 73 mg/dl and 5 with a2 macroglobulin < 110 mg/dl. The FT was done in parallel with liver biopsy with a fibrosis staging according to METAVIR (MV) classification in 33 HCV patients. When the FT fibrosis stage estimate was [3] 2 (i.e. 0.49-1), this was confirmed by MV in 14 of the 15 patients (93 %). When it was between 1 and 2, this was confirmed in 6 of the 6 patients (100 %). When it was < 2 (11 patients), MV was 0 or 1 in 6 but 5 patients (45 %) had discordant results : 4 MV2 and 1 MV3. FT area under the ROC curves for significant (F0-F1 vs F2-F4) and severe (F0-F1-F2 vs F3-F4) fibrosis was 0.80 and 0.88 respectively.
Conclusion, our external validation study confirm the excellent specificity of FT as a simple non-invasive quantitative estimate of significant liver fibrosis but it was inadequate to predict absence or minimal fibrosis.

[1]Rossi *et al.*, Clin Chem 2003

TRICOT : A PILOT STUDY ON THE SAFETY OF TRIPLE THERAPY WITH PEGINTERFERON ALFA-2A (40KD), RIBAVIRINE AND AMANTADINE IN HIV/HCV CO-INFECTED PATIENTS. J. Mulkay (1), K. Kabeya (2), S. De Wit (2), O. Van Der Meeren (3), N. Clumeck (2). (1) Hepatology ; (2) Infectious Diseases CHU Saint-Pierre Brussels, Belgium. ; (3) NV Roche SA Brussels Belgium.

Introduction : A substantial proportion of patients with HIV/HCV co-infection don't respond to the standard pegylated interferon/ribavirine (RBV) combination therapy. The usefulness of amantadine (AMA) as adjunctive therapy has been evaluated in several trials without conclusive response. Meta-analysis suggest that AMA could improve response rate in naïve mono-infected HCV patients (Mangia, J Hepatol 2004). Another meta-analysis didn't demonstrate any beneficial effect of AMA except in non-responders (Deltenre, J Hepatol 2004). Recent data show that AMA could reduce treatment-related fatigue (Formann, AASLD 2004). Data on this triple association are lacking in HIV/HCV co-infection.
Methods : an open-label prospective pilot study with peginterferon alfa-2a (40KD) 180µg qw plus ribavirin (RBV) 400mg bid plus amantadine (AMA) 100mg bid given for 48 weeks in HIV/HCV co-infected patients on stable HAART.
Results : 22 patients with chronic HCV infection and abnormal liver tests were enrolled, all naïve except 1 who failed previous IFN monotherapy. Baseline parameters were : median CD4 412 cells/µL, HCV-RNA 5.9 log IU/ml ; HCV genotypes were : 1 (8p, 36 %) ; 3 (3p, 14 %) ; 4 (11p, 50 %). METAVIR score was F0-F1 in 8p, F2 in 10p, F3-F4 in 3p (consistent with cirrhosis in 2p). At week 48, no unexpected adverse event was observed ; 4 had discontinued the study (2p for thrombocytopenia, 1 for > 10 % weight loss and 1 for psychiatric decompensation). Peginterferon alfa-2a (40KD) dose was reduced for thrombocytopenia (2p), asthenia (1p), depression (1p), and RBV for anemia (4p). G-CSF was used in 5p for neutropenia. The on-treatment median CD4 change was -265 cells/µL, and there were no change in HIV VL profile. At week 48, HCV VL was < 50IU/mL in 7/22p (32 %) and in 1/8 ; 2/3 and 4/11 for genotype 1, 3 and 4 respectively.
Conclusions : The combination of peginterferon alfa-2a (40KD) + RVB + AMA was safe and not associated with increased or unexpected toxicity. The global response was poor, but the number of p was small and the majority had genotype 1 or 4. These data illustrate the feasibility of this association allowing further evaluation for efficacy in HIV/HCV co-infected patients.

DEFECTIVE HEPATIC REGENERATION AFTER PARTIAL HEPATECTOMY TO LEPTIN DEFICIENT OB/OB MICE IS NOT RESCUED BY EXOGENOUS LEPTIN ADMINISTRATION. I. Leclercq (1), M. Vansteenberghe (2), V. Lebrun (1), P. Starkel (1), C. Picard (1), Y. Hosrmans (1). (1) Laboratoire de Gastro-entérologie, UCL, Brussels ; (2) Laboratoire de Chirurgie Experimentale, UCL Brussels.

Ob/ob mice have impaired liver regeneration attributed to leptin deficiency.
Aim : We tested the effects of leptin replacement on regenerative response to partial hepatectomy (PH) in ob/ob mice.
Methods : Activation of the priming phase and hepatocyte proliferation were analysed after a 55 % PH.
Results : 55 % PH to ob/ob mice was associated with defective regeneration : there were rare and significantly less mitotic figures, BrdU positive, Ki67 positive hepatocyte nuclei or PCNA up-regulation than in lean mice 44 hours after PH. Leptin replacement (100 µg/Kg body weight twice daily) restored normal circulating leptin levels and restrained the hyperactivation of transcription factors STAT-3 and AP-1 observed in ob/ob mice during the priming phase, but did not improve liver regeneration. Correction of the metabolic abnormalities of ob/ob mice (obesity, insulin resistance, hepatic steatosis) by food restriction (with or without leptin-repletion) or by leptin injections during 3 weeks prior to PH, similarly failed to induce any significant hepatocyte proliferation or expression of PCNA. Leptin is an important factor for macrophage and Kupffer cells function and cytokine production. The normal rise in hepatic TNF protein and IL-6 mRNA induced by PH was almost completely prevented in ob/ob mice. Moreover, exogenous leptin failed to correct TNF and IL-6 expression and to rescue liver regeneration after PH to *ob/ob* mice.
Conclusion : Liver regeneration is deeply impaired in *ob/ob* mice. We have conclusively shown that nor leptin replacement, nor attenuation of activation of transcription factors in the priming phase, nor amelioration of the metabolic syndrome and hepatic steatosis, with or without restitution of normal circulating levels of leptin, was able to restore replicative competence to *ob/ob* mice. All this strongly suggests that leptin does not directly signal on hepatocytes to allow the regenerative process. In addition, leptin replacement was not sufficient to favour the release of key cytokine mediators of proliferation such as TNF and IL-6. These results support the concept that leptin-deficiency renders the Kupffer cells (and maybe other liver cells) unable to release key mediators and cytokine to drive cell proliferation in the setting of partial hepatectomy.

ELEVATED HEPATIC VENOUS PRESSURE GRADIENT AND HEPATIC ARTERIAL HYPORESPONSIVENESS RELATED TO STEATOSIS IN METHIONINE-CHOLINE DEFICIENT DIET FED RATS. S. Francque (1), P. Pelckmans (1), A. Herman (3), E. Van Marck (4), P. Michielsen (1). (1) Laboratory of gastroenterology ; (3) Laboratory of pharmacology ; (4) Laboratory of pathology, Antwerp University, Antwerp, Belgium.

Background : Changes in splanchnic haemodynamics related to portal hypertension in cirrhosis are extensively studied. Arterial hyporesponsiveness has been demonstrated in the splanchnic and systemic circulation. Hepatic steatosis is evenso associated with haemodynamic changes, especially by reduction in portal venous flow, but these changes are poorly characterised.
Aims : Investigating wether steatosis causes portal hypertension and alterations in vascular responsiveness in a rat model of non-alcoholic steatohepatitis.
Material and methods : 12 male Wistar rats were fed a choline-methionine (MC) deficient diet (6) or a control diet (6) for 4 weeks. After induction of anesthaesia a catheter was inserted in the jugular vein and in the ileocolic vein to measure the hepatic venous pressure gradient. After sacrificing the rat, liver and spleen were removed and weighed. Biopsy samples of both liver lobes were taken. Abdominal and thoracic aortic rings were mounted in organ chambers filled with Krebs solution at 37°C and with continuous oxygenation. Dose-response curves to phenylephrine, after pre-contraction with potassium, were determined. Preservation of endothelial function was checked with acetylcholine, and dose-response curves to acetylcholine were also determined. Student t-test and non-linear best fit (SPSS 12.0) were used where appropriate.
Results : Biopsy confirmed the presence of severe steatosis in the MC diet-fed rats. Their liver/body weight ratio was significantly increased (4.71 ± 0.24 g vs 2.42 ± 0.18 g, p = 0.0001). The spleen/body weight ratio was not statistically different. The venous pressure gradient was higher in the MC diet-fed rats (10-11 mm Hg vs 1-3 mm Hg). The maximal contraction (expressed as % of potassium induced pre-contraction) was significantly lower in the MC diet group (120.4 %, 95 % CI : 116-124.7 %, vs. 151.9 %, 95 % CI : 144.9-159.0 % ; p = 0,008), as was the EC 50 (logEC50 8.55, 95 %CI : -9.51/-7.58 vs 7.20, 95 %CI : -7.36/-7.034 ; p = 0,032). No significant differences were demonstrated for the thoracic aorta.
Conclusions : In this animal model steatosis is associated with a significant raise in hepatic venous pressure gradient and hence with a certain degree of portal hypertension, and this is also associated with an arterial hyporesponsivenss in the abdominal but not in the thoracic aorta. The underlying mechanisms need to be elucidated.

A PILOT OBSERVATIONAL SURVEY OF HEPATITIS C IN BELGIUM. S. De Maeght (1), N. Bourgeois (2), C. de Galocsy (3), P. Langlet (4), P. Michielsen (5), H. Reynaert (6), G. Robaeys (7), D. Sprengers (8), M. Adler (9). (1) C. H. Jolimont ; (2) Hôpital Erasme ; (3) HIS Bracops ; (4) CHU Brugmann ; (5) UZ antwerpen ; (6) AZ VUB ; (7) Ziekenh. Oost-Limburg ; (8) CH St Augustinus, Antwerpen ; (9) Hôpital Erasme.

There is a lack of epidemiological data on hepatitis C (HCV) epidemics in Belgium. The aim of our study was to evaluate the feasibility of a national HCV observatory.
Methods :During one year (November 2003-November 2004), every new patient with HCV antibodies seen prospectively in 9 belgian centers by 17 hepatogastroenterologists was recorded and a standardized 10-item questionnaire was completed.
Results : Two hundred and sixty-five patients were recruited. ***Demographic and Clinico-biochemical characteristics*** were as follows : 55 % males ; median (IQR) age : 45 y (11-87) ; 86 % caucasians ; median (IQR) BMI and weight : 25 kg/m^2 (18-47)and 72 kg (46-137) ; risk factors for infection : IV drug use : 27 %, blood transfusion : 24 %, invasive medical procedures : 12 %, unknown : 22 %, other : 15 % ; year of first positive serology : < 1 : 46 %, 1-5 : 35 %, 6-10 : 12 %, 11-20 : 7 % ; discovery of HCV : fortuitous : 67 %, general symptoms : 27 %, extrahepatic signs : 5 %. Transaminases were normal in 34 %. Median elevation was 2 times normal value. On a QOL scale between 0-100, the mean was 61 ± 31 %. ***Virological data*** were as follows : RNA positive in 87 %, viral load above 800 000 IU/ml in 42 % ; genotype distribution : 1 : 60 %, 2 : 5 %, 3 : 19 %, 4 : 15 %, 5 : 2 %. ***Histological data*** showed : stage F0 : 12 %, F1 : 32 %, F2 : 34 %, F3 : 13 %, F4 : 9 % according to the Metavir classification. ***Antiviral treatment*** was proposed to 53 %. Reasons for non proposal included : normal ALT : 30 %, old age : 7 %, refusal : 3 % and others : 40 %.
Conclusions : This study highlights the feasibility of a national HCV survey using a simple questionnaire. This pilot study could be generalized throughout Belgium, allowing the follow up of the time-evolution of the epidemiological and medical characteristics of HCV.

THREE MONTHS DATA FROM THE PEGINTRUST STUDY : PEGINTRON IN COMBINATION WITH REBETOL IN REAL LIFE IN BELGIUM. M. Adler (1), B. Bastens (2), I. Colle (3), J. Delwaide (4), J. Henrion (5), Y. Horsmans (6), P. Michielsen (7), J. Mulkay (8), F. Nevens (9), W. Van Steenbergen (10), P. Yap (11), H. Van Vlierberghe (12). (1) Hôpital Erasme, Brussels ; (2) Hôpital St Joseph, Liège ; (3) UZ Ghent, Ghent ; (4) CHU Liège, Liège ; (5) Hôpital Jolimont, La Louvière ; (6) UCL St Luc, Brussels ; (7) UZ Antwerpen, Antwerpen ; (8) CHU St Pierre, Brussels ; (9) KULeuven, Leuven ; (10) KULeuven, Leuven ; (11) KULeuven, Leuven ; (12) UZ Ghent, Ghent.

The applicability, in real life, of the results from large international randomised therapeutic trials in hepatitis C, is not well known. In an independent observational study, 64 clinicians from 46 different Belgian general and academic hospitals included, from January 2003 till October 2004, 241 patients with genotype 1, 4 and 5 and suffering from significant fibrosis, for treatment with PEG-IFNa2b and ribavirin during 12 months The population consists of 55 % male patients, the median age is 51 (IQR 22-78) ; median weight is 74 kg (IQR : 45-120) ; median BMI is 25 kg/m^2 (IQR 17-42). Twenty three percent of the study group have an history of intravenous drug abuse ; 83, 14, and 3 % are patients with respectively genotype 1, 4 and 5 ; according to METAVIR 58, 22 and 20 % show respectively stage 2, 3 and 4 fibrosis and baseline viral load is above 800,000 IU/ml in 49 % of the patient population. Therapy had to be discontinued before the planned term and within the first 3 months of treatment in 21 patients (8.7 %). Reasons for withdrawal are non-compliance in 4 patients, adverse events in 11 and serious adverse events in 6 subjects. The median time lag between starting and stopping treatment is 73 days (IQR 18-99). One patient died from septic shock and multiple organ failure. Early virological response (EVR) is 67 % i.e. observed in 95 patients out of 141, for whom all virological data are available at month 3. From these preliminary data, we can conclude that, compared to the Mann’s trial (1) and the Davis’ analysis (2), Belgian patients treated in real life are leaner, older, suffer from more advanced fibrosis while achieving similar EVR and lower early treatment discontinuation rate.

1 Lancet 2001 ; 2 Hepatology 2003.

- B 01 -

COMPARATIVE EVALUATION OF FETAL DIGESTIVE SYNGENIC IMPLANTS FUNCTIONAL CAPACITIES (EXPERIMENTAL STUDY). V. Coulic (1), E. DeKoster (1), P. Delrée (2), P. Deltenre (1), C. DePrez (1), N. Hermanus (1), M. Krzemien (1), V. Novikov (3), B. Sidi (1). (1) CHU Brugmann, ULB,Brussels ; (2) IPG, Loverval ; (3) Institut de Transplantation, Moscou.

The interest for fetal digestive organ and cell implantation as therapeutic means in the treatment of some gastric, intestinal,liver and pancreatic diseases is presently increasing. The aim of the present investigation was the comparative evaluation of the functional potential of ectopically grown fetal digestive organs.
Material and methods. 244 Rats were used. Donors were fetuses aged 15- 20 days i.u. Recipients were syngenic adult rats. Fetal intestines, stomach, pancreas and liver were chosen as implants, taking on account their different physiological role in digestion and possible clinical applications. A unified operative model was the fetal organ fragment implantation into an ear subcutaneous pouch The implant isolation outside of the organism varied from 15 to 50 min. As control, intact animals were used as well as animals with streptozotocin diabetes and hepatic lesions due to the main bile duct ligature. The functional capacities of the implants were tested by electrogastrography, echography, evaluation of blood and urine glucose and protein levels, pH measure of the stomach and intestine contents,optic and electronmicroscopy,histochemistry, immunohistochemistry. Observation periods extended up to 14 months. Student and Chi-2 statistical criteria were used.
Results.I month after operation, fetal intestine implants looked well-developed adult structures with secretion, absorption and motor functions. Later on (6-12 months), retention cysts developed and functional regression was noted. Fetal stomach implants followed the same pattern as fetal intestine. When implanted with the lower third of the esophagus, a fistula formed between the growing stomach lumen and the skin, which prevented the retention process. The implant "gastric juice" remained neutral. Acidification of its pH was observed only after introduction into its lumen of albumin solution especially. Fetal pancreas implants developed only duct and endocrine tissue. Endocrine function was proved by correction or improvement of Streptozotocin induced diabetes in 32 % of all the cases. Factors improving these results were : controlled glycaemia between 200 and 300 mg/l and increased implanted fetal organ mass. After fetal liver implantation both bile ducts and hepatocytes columns developed but bile formation was not found. In the case of main bile duct ligature, the fetal liver implant development was enhanced and the recipient early survival was improved.
Conclusion, implanted and ectopically grown digestive fetal organs expressed functional activity. The best adult-like function was obtained in intestinal and gastric implants, that is in organs with a cavity and a well-developed self-regulation system. The worse results were obtained inmajor digestive gland implants - pancreas and liver, maybe, because of important regional endo- and paracrine influences missing in the experimental model tested.Soclinical applications need further organ specific approach.

- B 02 -

OPTICAL RECORDING OF FEPSP-LIKE ACTIVITY IN THE ENTERIC NERVOUS SYSTEM OF THE GUINEA-PIG ILEUM. A. Sini, P. Vanden Berghe, J. Janssens, J. Tack. Center for Gastroenterological Research, lab. 701 KULeuven.

To expand the current understanding of gastrointestinal motility control we have developed an optical method, based on Ca2+ indicators to register activity in the enteric nervous system (ENS) (Vanden Berghe *et al*. 2000). So far this technique was well suited to record activity induced by exogenously applied ligands, such as substance P, acetylcholine, CRF and ghrelin (Bisschops *et al*. 2004) or by trains of electrical stimuli (2s, 15-30Hz) known to elicit slow excitatory postsynaptic potentials (EPSP). Here, we adapted the technique and analysis routines to also detect activity in whole mount tissue induced by single stimuli (0.5 ms) that elicit fast EPSPs. Methods : We dissected standard longitudinal myenteric plexus preparations that we loaded with Fluo-4 AM (9 μM, 45 min at RT). Tissues were mounted on a metal ring and transferred to a cover-glass bottom chamber. Ca2+ movies (512 × 480) were recorded at 7.5Hz with a Noran confocal microscope and stimuli were applied with a focal electrode carefully placed on one of the fiberstrands. All analysis was performed with custom-written routines in Igor Pro (Wavemetrics). Results : Since experiments were performed at room temperature spontaneous [Ca2+]i signaling events were rare. However a single electrical shock elicited activity in both fiberstrands and ganglia. Generally, a stimulus caused a fast flash within the ganglion (n = 7) followed by a transient rise in some individual cells. Activity in ganglia and adjacent muscle could be measured simultaneously. We found that nerves always preceded muscular [Ca2+]i activity (~1.2s) and contraction (~2.8s). Activity was often perceived as a flash because the signal in fibers easily reached detection threshold, while in the cell body overall Ca2+ concentrations remain often too low. Within the ENS network, activity could be detected up to 5 ganglion rows (~ 2 mm) from the stimulating electrode. However not all ganglia in between were active, indicating that specific neuronal pathways were stimulated. Conclusion : We can now optically record activity equivalent of fEPSP's, thereby this technique has become a promising tool to map spread of fast activity throughout the ENS and link it to activity in adjacent muscle cells. Support : FWO, Vlaanderen.

- B 03 -

MOLECULAR DIVERSITY OF POTASSIUM CHANNELS IN MURINE SPINAL AND VAGAL VISCERAL AFFERENTS. P. J. Peeters (1), J. Aerssens (1), K. Hillsley (2), R. de Hoogt (1), A. Stanisz (2), D. Grundy (2), R. H. Stead (2), B. Coulie (1). (1) J&J Pharmaceutical Research and Development, Beerse, Belgium ; (2) Holburn Group, Bowmanville, Ontario, Canada.

Background : K^+ channels are a large and diverse family of ion channels that play an important role in maintaining membrane potential and modulating neuronal excitability. This diversity is generated both by the large number of genes encoding subunits and by their heteromeric composition. The aim of this study was to evaluate murine K^+ channel subunit expression in dorsal root (DRG) and nodose ganglia (NG) projecting to the gut.
Methods : Intraperitoneal injection of Cholera toxin B-488 in 11 Balb/c mice identified neurons projecting to the gut. Fluorescent neurons in DRG (T10 to T13) and NG were isolated using laser capture microdissection. Labelled RNA was hybridised to Affymetrix Mouse whole genome arrays. Differential expression was defined as at least 1.5 fold difference (FD) in expression and false discovery rates were calculated using significance analysis method for microarray data (SAM) and expressed as a q-values.
Results : Arrays allowed detection of mRNA expression levels of 133 K^+ channel subunits, of which only 44 K^+ channels were reliably detected in DRG or NG. Of these 23 were equally expressed in DRG and NG, 16 had significantly ($q < 0.01$) higher expression in DRG and 5 were higher in NG. With respect to Ca^{2+}-dependent channels, the principal subunits encoding SK2, IK1 and BK channels were equally present in DRG and NG neurons, as well as the BK auxiliary subunit Sloß4. The SK1 channel, BK auxiliary Sloß1 and Sloß2 subunits were primarily detected in DRG. $K_v4.3$ A-type K^+ current was equally distributed, whereas $K_v1.4$ and $K_v4.1$ were expressed more in DRG and $K_v3.4$ was higher in NG. Regarding inwardly rectifying currents, Kir3.1, Kir4.1 and Kir4.2 were equally expressed, whereas $K_{ir}2.4$ was higher in DRG, and $K_{ir}3.3$ was slightly higher in NG ($q = 0.04$). Slow delayed rectifiers mediating M-type K^+ currents are encoded by *Kcnq2*, *Kcnq3* and *Kcnq5*. All three subunits are available to form heteromeric channels in DRG, whereas only *Kcnq2*/*Kcnq3* are present in NG. With respect to two-pore domain channels, both Trek-1 and Traak were present in DRG and NG but Trek1 expression levels were higher in DRG (2.5 FD).
Conclusions : These data provide a catalogue of K^+ channels subunits present in NG and DRG neurons supplying the gut and demonstrate clear differences in K^+ channel expression. These divergences may underlie the contrasting roles of NG and DRG, and contribute to differences in the control of excitability between these visceral sensory neurons.

- B 04 -

HIDDEN FOCAL ABNORMALITIES OF SMOOTH MUSCLES IN HUMAN GI MOTILITY DISORDERS REVEALED BY NOVEL IMMUNOMARKERS. T. Wedel (1), G. van Eys (2), W. Glénisson (3), D. Waltregny (3), J. M. Vanderwinden (4). (1) Institute of Anatomy, University of Luebeck, Luebeck, Germany ; (2) Department of Molecular Genetics, University of Maastricht, Maastricht, Netherlands ; (3) Metastasis Research Laboratory, University of Liège, Liège, Belgium ; (4) Laboratory of Neurophysiology, Faculté de Médecine, Université Libre de Bruxelles, Brussels, Belgium.

Background & Aims : Pathology in gastrointestinal (GI) motility disorders mainly focused on the enteric nervous system and, more recently, on the interstitial cells of Cajal. Smooth muscle cells have been considered only occasionally. Here we have assessed several classical and two novel smooth muscle markers in human GI motility disorders. Methods : Full thickness biopsies from chronic intestinal pseudoobstruction, Hirschsprung´s disease, idiopathic megacolon, slow-transit constipation, duodenal atresia, cardia achalasia in Algrove's syndrome (3A) and from controls were stained with H&E and with antibodies against a-smooth muscle actin (SMA), smooth muscle myosin heavy chain (SMMHC), histone deacetylase 8 (HDAC8) and smoothelin (SM).
Results : Smooth muscle layers from controls and 3A exhibited a homogeneous immunoreactivity (-ir) for all antibodies. In the other diseases, H&E showed a normal morphology and SMA-ir was generally inconspicuous while, in a subset of cases, SMMHC-ir, HDAC8-ir and/or SM-ir were either lacking or presented a patchy pattern. Noteworthy, these markers were not always concordant. Muscularis mucosae and blood vessels were consistently evenly stained in all cases. Conclusions : In a subset of patients with various GI motility disorders, the novel smooth muscle immunomarkers SM and HDAC8 exposed striking abnormalities, which were not detected by both routine histopathology and SMA-ir. The pathophysiological mechanism leading to the loss of expression of these new markers and its functional consequence on motility remain to be unravelled. However, these data emphasize that a detailed appraisal of the smooth musculature broadens the spectrum of morphologic correlates in GI motility disorders.

- B 05 -

GENE EXPRESSION PROFILES IN VISCERA-SPECIFIC NEURONS ARE ALTERED IN NODOSE GANGLIA (NG) BUT NOT DORSAL ROOT GANGLIA (DRG) IN A POST-INFECTIOUS MODEL OF IRRITABLE BOWEL SYNDROME (IBS). J. Aerssens (1), P. Peeters (1), R. de Hoogt (1), K. Hillsley (2), A. Stanisz (2), D. Grundy (2), R. Stead (4), B. Coulie (1). (1) J&J Pharmaceutical Research and Development, Beerse, Belgium ; (2) Holburn Group, Bowmanville, Ontario, Canada.

Background : Extrinsic afferent neurons supplying the gut are prime targets for new treatments of chronic visceral pain disorders such as IBS. The pathogenesis of IBS is heterogeneous but at least in a subpopulation of patients emotional stress and enteric infection have been implicated. The aim of this study was to investigate long term changes in gene expression in both NG and DRG in a mouse model of IBS. The model consisted of a transient inflammation induced by the nematode *Nippostrongylus brasiliensis* (Nb) combined with exposure to stress.
Methods : Balb/c mice housed in control / stress conditions were infected with 500 L3 Nb larvae. After 21 days NG and DRG (T10-13) were removed in addition to jejunal sections (mast cell counts) and sera (IgE levels) to confirm infection. Gut-specific neurons labeled by intraperitoneal injection of cholera toxin B-488 were isolated by laser capture microdissection. Labeled RNA was hybridized to Affymetrix murine arrays with 39,000 transcripts, and expression of key genes was confirmed with RTq-PCR. Expression profiles were analyzed by multivariate spectral map analysis and significance analysis of microarray data algorithm (SAM). Differentially expressed genes were defined by a combination of : ≥ 1.5 fold difference in expression level ; < 10 % false discovery rate ; and/or positioning at the extremities of the spectral map.
Results : None of the transcripts was differentially expressed after Nb infection in viscera-specific DRG neurons. In contrast in NG neurons, significantly different expression levels were found for 1994 genes after Nb infection, 1377 of which were increased and 617 were decreased. Altered NG genes included 19 G-protein coupled receptors, 23 ion channel genes, 80 kinases, and 118 other receptor-related genes. For example, cholecystokinin receptor A (*Cckar*) was upregulated in Nb infected NG neurons, whilst serotonin receptor 3A (*Htr3a*) was downregulated (confirmed by RTq-PCR). Interestingly, the effect of Nb infection alone on expression level of these genes was enhanced in infected stress-exposed animals.
Conclusion : Surprisingly no long-term changes in gene expression were recorded in DRG neurons. However, a plethora of genes are altered in NG neurons by Nb infection and stress, at a time point when the acute inflammation has subsided. Conversely, These findings may impact our view of post-infectious models of IBS.

- B 06 -

REPEATED ACUTE ESOPHAGITIS, PATTERNS OF INFLAMMATION AND ESOPHAGEAL DYSMOTILITY. X. Zhang (1), K. Geboes (2), I. Depoortere (1), J. Tack (1), J. Janssens (1), D. Sifrim (1). (1) Center for Gastroenterological Reserch, KUL ; (2) Department of Pathology, University Hospitals, KUL.

Acute experimental esophagitis provokes severe but reversible hypomotility. Reflux disease in man involves repeated episodes of mucosal inflammation and spontaneous or treatment-induced healing. However, severe esophagitis-hypomotility in man is mostly irreversible. Spaced repeated experimental acute esophagitis provokes milder motor effects suggesting an adaptive response. The **aim** of this study was to further characterize such adaptive mechanism.
Methods : Repeated acute esophagitis (every 8 weeks) was induced by intraluminal acid perfusion (0.1N HCl, 80min) on 8 adult cats. Esophageal motility, tone and shortening were assessed before and after each perfusion. The degree of esophageal mucosal damage was evaluated with endoscopy, histology and MPO activity measurements.
Results : Acid perfusion induced severe esophagitis. At 24hs, distal peristaltic contractions disappeared ; LES pressure was reduced by 60 % ; esophageal length was 1-2 cm shorter and esophageal compliance was reduced by 30 %. Most parameters recovered in 4 weeks. Subsequent repeated acute injuries induced milder motor disturbances. Identical endoscopic esophagitis (grade III) was observed after the first and second acid perfusions. The injurie after the first and second acid perfusions was extensive, involving the entire depth of the mucosa and the major part of the surface. However, with the second acid perfusion the inflammatory infiltrate was less intense, more mononuclear cells were present and mainly located in the deeper part of the lamina propria. The inflammatory reaction was less pronounced or absent at the level of the muscularis propria and the level of MPO activity was lower (10.5 ± 1.9 MPO units/mg vs. 3.1 ± 0.5 MPO units/mg). In spite of endoscopic appearance of complete healing 8 weeks after the first acute esophagitis, the histological examination showed fibrosis of the lamina propria and the muscularis mucosae with loss of smooth muscle cells, and to a lesser extent, changes of the submucosa.
Conclusions : Subsequent repeated acute injuries induce similar endoscopic esophagitis but different pattern of inflammatory infiltration and fibrosis resulting in milder motor disturbances. In patients with severe esophagitis-induced irreversible dysmotility such mechanism is not present or is overcome by the inflammatory reaction.

- B 07 -

INFLUENCE OF ONDANSETRON ON GASTRIC SENSORIMOTOR RESPONSES TO DUODENAL ACID INFUSION. T. Vanuytsel, G. Karamanolis, R. Vos, J. Janssens, J. Tack. Gastroenterology Department, UZ Gasthuisberg.

Recently, we reported increased duodenal acid exposure in a subgroup of functional dyspepsia (FD) patients with higher symptom scores. In healthy controls, duodenal acidification induces gastric relaxation and sensitizes to gastric distension (Lee 2003, 2004). Animal studies have shown that acid releases 5-hydroxytryptamine (5-HT) from duodenal enterochromaffin cells, which may activate 5-HT3 receptors on vagal chemosensitive afferents and motor stimulating pathways (Kellum 1976).
The aim of this study was to investigate involvement of 5-HT3 receptors in duodenal acidification-induced changes in gastric sensorimotor function.
Methods : Fourteen healthy volunteers (6 men, mean age 24) were studied on 2 occasions, at least one week apart. An infusion tube with attached pH electrode was positioned in the second part of the duodenum, and a barostat bag was located in the gastric fundus. Proximal stomach tone and sensitivity to distension were assessed before and during duodenal acid infusion of 0.1 N HCl, after pre-treatment saline or the 5-HT3-receptor antagonist ondansetron 8 mg i.v. in a randomized, double-blind, cross-over fashion. Duodenal pH-measurement and assessment of nine epigastric symptoms, on 100-mm visual analogue scales (VAS), were obtained from all volunteers. Results are given as mean ± SEM and compared by Student's t-test and two-way ANOVA.
Results : Intraduodenal pH-measurements showed no difference after ondansetron or placebo. Ondansetron had no influence on the duodenal acid acid-induced gastric relaxation and increase in gastric compliance. After saline pretreatment, duodenal acidification significantly increased perception scores during gastric distention (ANOVA, $p < 0.05$), and this was inhibited by ondansetron pre-treatment. During acidification, symptom scores for discomfort (14 ± 1 vs 19 ± 0.4, $p < 0.005$), bloating (11 ± 0.7 vs 17 ± 0.4, $p < 0{,}005$), fullness (12 ± 0.5 vs 17 ± 0.7, $p < 0.005$), satiety (13 ± 0.4 vs 15 ± 0.2, $p < 0.05$), and heartburn (2.8 ± 0.1 vs 4.7 ± 0.3, $p < 0.001$) were significantly lower after ondansetron pre-treatment compared to placebo. Conclusion : 5-HT3-receptors are involved in duodenal acid-induced gastric sensitisation and symptom generation, but not in the acid-induced duodeno-gastric inhibitory motor reflex. 5-HT3-receptor antagonists have a potential role in the treatment of FD patients with increased duodenal acid exposure.

- B 08 -

DIFFERENTIAL EFFECTS OF 5-HT4 RECEPTOR AGONISTS AT GASTRIC VERSUS CARDIAC 5-HT4 RECEPTORS. J.H. De Maeyer (1), R. Straetemans (2), J.A. Schuurkes (3), R.A. Lefebvre (1). (1) Heymans Institute of Pharmacology, Ghent University, Ghent, Belgium and Johnson & Johnson Pharmaceutical Research and Development, Beerse, Belgium ; (2) Limburgs Universitair Centrum, Center for Statistics, Biostatistics, Diepenbeek, Belgium ; (3) Johnson & Johnson Pharmaceutical Research and Development, Beerse, Belgium.

Stimulation of 5-HT_4 receptors on gastric cholinergic nerve endings leads to enhanced cholinergic neurotransmission, while stimulation of 5-HT_4 receptors on cardiac cells may lead to inotropic and chronotropic effects. We therefore analysed in vitro the possible differential effects of the 5-HT_4 receptor agonists prucalopride, tegaserod, JNJ 17303910 and JNJ8072285 and the natural ligand 5-HT in porcine (25 kg pigs) stomach and heart. Longitudinal muscle strips from the ventral side of the proximal stomach (PS) and left atrial pectinate muscles (LA) were mounted in organ baths (resting tension : PS : 2g, LA : 50 % of the length at which maximal contractions occurred) supplemented with, 0.1mM N^G-nitro-L-arginine-methylester and 1µM indomethacine (PS) or with 0.2µM propranolol, 6µM cocaine and 20µM IBMX (LA). Tissues were electrically stimulated (PS : 4Hz, 0.5ms, voltage to obtain half maximal contractions ; LA : 0.5Hz, 5ms, just above threshold voltage) and agonists were added cumulatively. Effects were quantified as % increase of electrically induced contractile force per se (PS) or relative to the increase caused by 0.1mM isoprenaline (LA). Data were analysed using non linear mixed effects models (PROC NLMIXED ; SAS). For all the agonists under study, EC50 values were significantly smaller in PS than in LA (LA/PS ratios ranging from 4.0 for prucalopride to 11.9 for tegaserod), while only prucalopride showed a significantly higher maximal effect in PS (LA/PS ratio of 0.75). In PS, the EC_{50} and Emax of prucalopride and tegaserod did not significantly differ from that of 5-HT, while in LA the Emax of prucalopride was smaller than that of 5-HT and tegaserod was less potent than 5-HT. Both in PS and LA, JNJ17303910 and JNJ8072285 were more potent than 5-HT but their Emax was smaller. These results indicate that differential effects between porcine left atrial and proximal stomach 5-HT_4 receptors are obtained with prucalopride and tegaserod. This might be related to differences in binding or coupling profiles of these agonists in the two tissues, possibly associated with a distinct splice variant population. The data are actually being analysed according to the operational model of agonism to address this issue.

- B 09 -

EVIDENCE FOR DIRECT INTERACTION BETWEEN HUMAN CCK2R AND RGS2. I. Langer (1), I. Tikhonova (2), S. Vatinel (2), A. Ferrand (2), F. Lopez (3), JP. Estève (3), C. Boulègue (4), D. Fourmy (2). (1) Laboratoire de Chimie Biologique et de la Nutrition, Faculté de Médecine, ULB, Brussels, Belgium ; (2) INSERM U531, Toulouse, France ; (3) IFR31, Toulouse, France ; (4) Max-Plank-Institut, Martiensried, Germany.

CCK2 receptor is a seven transmembrane domain receptor preferentially coupled to Gaq protein that stimulates phospholipase C and that binds with high affinity both cholecystokinine (CCK) and gastrin. In the periphery, CCK2R regulate acid and histamine secretions as well as growth in the gastric mucosa and gastrointestinal motility. Recently, it has been demonstrated that RGS proteins played a crucial role in G Protein Coupled Receptor (GPCR) mediated signalling. Regulators of G-protein signalling (RGS proteins) are a family of diverse, multifunctional proteins that share a conserved 120 amino acid domain (RGS box). RGS box binds directly to activated Galpha subunits and acts as GTPase-activating proteins (GAPs) to attenuate and/or modulate GPCR mediated signalling. The mechanisms by which individual RGS proteins desensitize pathways activated by particular GPCRs remain to be elucidated. We and others hypothesized that, in addition to RGS box, other domains of RGS contribute to targeting of individual RGS proteins to particular receptor. For that purpose, we constructed amino-terminally truncated RGS2, over-expressed them in COS-7 cells and evaluated their inhibitory effect on CCK2R mediated inositol phosphate accumulation. We found that removal of the 80 amino acids preceding the RGS box completely abolish RGS2 activity but that activity was restored by adding the sequence comprised between residues 54 and 80 of RGS2. The same approach was used to identify potential CCK2R domains involved in direct interaction with RGS2 and found that removal of a 10 amino acids sequence (429-439) in carboxyl-terminus tail of CCK2R abolish inhibitory effect of RGS2. Pull down experiments confirmed that RGS2 and CCK2R interact together and that the identified sequences were directly involved. These results allowed us to build a 3D model of [RGS2.CCK2R] complex and to propose the amino acids responsible for direct interaction between RGS2 and CCK2R.

- B 10 -

STRUCTURAL REQUIREMENTS AND PHARMACOLOGY OF HUMAN RECOMBINANT VPAC1 RECEPTOR INTERNALIZATION AND TRAFFICKING. Nachtergael, C. Langlet, I. Langer, P. Robberecht. Laboratoire de chimie biologique et de la nutrition ULB.

VPAC1 receptor (one of the common VIP/PACAP receptors) is rapidly desensitized and internalized after exposure to VIP or agonists. Internalization can be followed by flow cytometry using a monoclonal antibody recognizing the extracellular amino-terminal domain of the receptor without interference with VIP binding and agonist activation. In stably transfected CHO cells expressing the wild type receptor, up to 80 % of the receptors are internalized within 5 to 30 minutes after VIP exposure. It is generally admitted that this is due to successively receptor phosphorylation, ^{2}-arestin interaction and clathrin dependent endosome formation and that the receptors may be recycled to the membrane or degraded in lysosomes depending on their affinity for ^{2}-arestin. After internalisation the VPAC1 receptor is not reexpressed at the membrane. Mutation of all the phosphorylable ser/thr residues abolished receptor internalization. However truncation of the carboxyl terminus allowed receptor internalization even in absence of phosphorylation followed by a rapid recovery. We hypothesized that carboxyl functions of Asp or Glu residues can mimic phosphoryl groups. Receptors mutated in TM3 and TM7 (N229A VPAC1 and Q380A VPAC1) had a moderately reduce VIP potency, a normal phosphorylation, a normal internalisation rate but also a receptor recovery. A similar profile was observed when one of the phosphorylated residues (T429) in the carboxylic terminus was replaced by a glutamic acid. The recovery of the internalized receptors was not detected when internalization was induced with the super agonist [R16-VIP]. In conclusion, internalization/recovery of the VPAC1 receptor after agonist exposure may be induced by different receptor domains. Their accessibility depends on the length of the carboxy terminus as well as on the efficacy of the agonist used.

MORE POTENT DESENSITIZATION AND SLOWER RESENSITIZATION OF THE MOTILIN RECEPTOR FOLLOWING STIMULATION WITH THE MOTILIDE ABT-229 THAN WITH MOTILIN. Mitselos, I. Depoortere, T. Peeters. University of Leuven.

Background. Recent studies showed that there is a difference in the ability of motilin and the motilide ABT-229, to induce desensitization and internalization of the motilin receptor (MTLR) (Thielemans, L., Gastroenterology, 124 :A1, 2003). This study aimed to examine whether there is also a difference in their resensitization kinetics.
Methods. Agonist induced Ca^{2+} luminescence was studied in Chinese hamster ovary (CHO-K1) cells expressing the MTLR and the Ca^{2+} indicator apoaequorin (Euroscreen, Belgium). Cells were desensitized by incubation for 2 hours with different concentrations (10^{-4}-10^{-12}M) of motilin and ABT-229 prior to a second stimulation with motilin. The pretreatment concentration which reduced the response to 50 % of the control response (no preincubation) was calculated (pDC_{50} value). For resensitization, cells were incubated with motilin (10^{-6}-10^{-8}M) and ABT-229 (10^{-6}-10^{-9}M) for 2h, washed and kept at 37°C for 0, 2, 4, 8, 12, and 24h. The maximal Ca2+ response of pretreated cells to a second stimulation with motilin was expressed as a % of the maximal response of untreated cells and the time at which 50 % of the receptors reappeared (t1/2) was calculated.
Results. Although motilin is more potent than ABT-229 in activating the cells (pEC_{50} : 9.64 and 8.88 resp.), it is less potent in inducing desensitization (pDC_{50} : 7.85 and 8.89 resp.). From these data, concentrations were estimated which for both compounds led to ~40 %, ~75 % and.~90 % desensitization, i.e. motilin (10^{-8}M, 10^{-7}M and10^{-6}M) and ABT-229 (10^{-9}M, 10^{-8}M and10^{-7}M). Following pretreatment at these concentrations, the resensitization t1/2 was approximately 1.71h, 2.36h, 5.63h for motilin and 2.11h, 3.63h, 12.12h for ABT-229. Resensitization 24h after stimulation with 10^{-7}M motilin (92 ± 3 %) or ABT-229 (68 ± 6 %) was not affected by pretreatment of the cells with the protein synthesis inhibitor cycloheximide (1 µg/ml) (motilin : 9 ± 3 %, ABT-229 : 68 ± 6 %).
Conclusion. Not only has ABT-229 a higher potency to desensitize, resensitization is also slower after desensitization with ABT-229. For both compounds resensitization is due to recycling and does not require de novo synthesis of the receptor.

THE RABBIT SMALL INTESTINE SHOWS REGIONAL DIFFERENCES IN BASAL TONE DEVELOPMENT AND IN SENSITIVITY TO MOTILIN. E. Ghoos, K. De Houwer, L. Ver Donck, J. Schuurkes. Johnson and Johnson Pharmaceutical Research and Development, a Division of Janssen Pharmaceutica NV.

Background : The rabbit duodenum is the tissue of choice to study motilin agonism *in vitro*. However, rabbit duodenal segments show a time-dependent increase in basal tone which complicates studies over prolonged periods of time. The aim of this study was : 1) to investigate changes in basal tone of segments from different parts of the small intestine after prolonged stabilisation, and 2) to determine the effect of motilin on these segments.
Methods : New-Zealand white rabbits of either sex (~2 kg) were euthanised and the entire small intestine was isolated. Segments (30 mm long) were dissected from 8 sites along the small intestine and were mounted vertically in organ baths for isotonic contraction measurements (Tyrode solution, 95 % O_2 + 5 % CO_2, 37 °C, 2 g preload). After 1 h of stabilisation, the preparations were exposed to cumulative increasing concentrations of carbachol (10^{-9} M to 3.10^{-6} M). After wash out and another 1 h of stabilisation, cumulative increasing concentrations of motilin (3.10^{-11} M to 3.10^{-7} M) were added. Contractions were expressed as % of the maximal preceding contraction to carbachol. Change in basal tone was expressed in mm contraction.
Results : Responses to carbachol did not differ over the various segments. Oral segments showed a spontaneous increase in basal tone whereas it remained stable in segments at ^{3}70 cm from pylorus (table, mean ± sem, n = 4). Motilin induced concentration-dependent contractions in all segments, but efficacy and pEC_{50} decreased aborally.

Dist. from pylorus (cm)		10	30	50	70	90	130	170	210
D basal tone (mm)		6.6 ± 2.0	5.1 ± 2.2	0.5 ± 0.7	0	0	0	0	0
motilin	30 nM (%eff)	68 ± 2	53 ± 11	69 ± 2	60 ± 7	38 ± 5	28 ± 2	15 ± 4	2 ± 1
	pEC_{50}	8.6 ± 0.1	8.6 ± 0.2	8.3 ± 0.0	8.1 ± 0.1	7.9 ± 0.1	7.8 ± 0.1	7.5 ± 0.1	7.1 ± 0.1

Conclusion : Rabbit small intestinal sensitivity to motilin decreases aborally. An optimum between stable basal tone and motilin sensitivity is reached at 50-70 cm from the pylorus.

EFFECT OF CAPSAICIN ON IMPAIRED GASTRIC EMPTYING IN RATS WITH TNBS-INDUCED COLITIS. H. De Schepper (1), J. De Man (1), T. Seerden (1), L. Van Nassauw (2), A. Herman (3), J. Timmermans (2), P. Pelckmans (1), B. De Winter (1). (1) UA Division of Gastroenterology ; (2) UA Division of Cell Biology and Histology ; (3) UA Division of Pharmacology.

Background : Patients with IBD often suffer from impaired gastrointestinal motility, even at sites remote from the inflammation. A role for sensitization of neural pathways has been suggested but remains poorly understood. The **aim** of the present study is to exclude systemic inflammatory modulation and to test the involvement of extrinsic reflex pathways in the impaired gastric emptying in rats with TNBS colitis.
Methods : Distal colitis was induced in Wistar rats by rectal instillation of 30 mg trinitrobenzene sulphate (TNBS) in 50 % ethanol 72 h prior to experiment. Myeloperoxidase (MPO) measurements were performed in the gastric fundus and distal colon to assess neutrophil infiltration. To examine systemic TNBS induced effects on smooth muscle contractility, aortic rings were contracted *in vitro* with phenylephrine (1nM-10 $^{1}/_{4}$M) and KCl 50 mM. *In vivo*, gastric emptying and intestinal transit were measured after intragastric instillation of a semi liquid bolus of Evans blue. Extrinsic afferent innervation was defunctionalized by treating rats with capsaicin (50 mg/kg SC) two weeks prior to experiments and controlled immunohistochemically.
Results : MPO activity was significantly increased in the distal colon of TNBS-treated animals from 4.7 ± 0.9 U/g in controls to 146.3 ± 33.9 U/g in TNBS rats (n = 6). However, MPO activity in the gastric fundus was not affected by induction of colitis. Aortic contractions to phenylephrine were identical in saline vs. TNBS-treated rats. Aortic contractions to KCl were unaffected. *In vivo* TNBS induction caused a significant decrease in GE from 33.1 ± 5.2 % in controls to 19.2 ± 2.3 % in TNBS rats (n > 7). TNBS had no significant effect on intestinal transit. Capsaicin pretreatment reduced GE by 71 % in control rats to 9.5 ± 3.3 %. However, in TNBS rats, the effect of capsaicin on GE was not longer significant (40 % reduction to 11.5 ± 3.8%). Capsaicin treatment had no significant effect on the geometric center while the front of migration of Evans blue was significantly delayed in the small intestine.
Conclusions : We showed that TNBS colitis induces a pronounced gastroparesis which is not associated with inflammatory changes in the gastric fundus or systemic impairment of vascular smooth muscle activity. The reduced effect of capsaicin in TNBS rats suggests a possible role for extrinsic afferent pathways.

INVOLVEMENT OF MUCOSAL MAST CELLS IN PERMEABILITY CHANGES OF THE INTESTINAL EPITHELIUM AFTER SCHISTOSOMA MANSONI INFECTION. F. De Jonge (1), J. Brown (2), L. Van Nassauw (1), A. Kroese (3), H. Miller (2), E. Van Marck (4), J. Timmermans (1). (1) Lab. Cell Biology and Histology, University of Antwerp, Belgium ; (2) Dept. Veterinary Clinical Studies, University of Edinburgh, Scotland ; (3) Dept. Medical Physiology and Surgery, UMC Utrecht, The Netherlands ; (4)Lab. Pathology, University of Antwerp, Belgium.

Schistosomiasis is a chronic parasitic disease caused by flukes of the genus *Schistosoma* and accompanied by motility-related gastro-intestinal disorders. We previously reported an upregulation of mucosal mast cells (MMC) in the lamina propria of the infected intestine (De Jonge *et al*., 2002) and hypothesized that an increase of MMC in the epithelial layer and subsequent release of mouse mast cell protease-1 (mMCP-1) might cause an increased epithelial permeability resulting in an enhanced egg clearance from the gut wall to the lumen. Two main questions are addressed in the present study : 1) Does intestinal mastocytosis in schistosomiasis involve enhanced recruitment of mast cell precursors from the bone marrow and peripheral blood or is this mastocytosis exclusively due to differentiation of precursors present in the gut wall ? 2) Are these MMC able to affect the integrity of the intestinal epithelial barrier ? We used limiting dilution assay (LDA) to investigate the source of mast cell precursor (MCp) cells giving rise to intestinal mastocytosis after *S. mansoni*-infection. Faecal and intestinal egg counts of infected mMCP-1-knock out (KO) and -wild type (WT) mice were performed to determine a possible involvement of MMC in egg expulsion. The effect of mMCP-1 on the integrity of the epithelial barrier was investigated by means of immunohistochemical staining for tight junction proteins. LDA revealed a higher number of MCp frequencies in the bone marrow and peripheral blood of infected animals. These data support the hypothesis that in response to an infectious challenge the bone marrow itself responds by producing committed precursors, thereby making quantitative decisions about the required hematopoietic response. Immunostaining for mMCP-1 and mMCP-2 revealed that both markers were present in infected WT animals, whereas only mMCP-2-immunoreactivity was observed in mMCP-1 KO mice. Staining for the tight junction proteins occludin, claudin and ZO-1 clearly demonstrated the presence of continuous hexagonal structures around the apices of the epithelium in non-infected animals. In contrast, in acutely infected animals, a fragmental staining pattern of these tight junction proteins was observed, indicating a deterioration of the tightness of the epithelial barrier. This phenomenon was not seen in acutely infected mMCP-1-KO animals pointing to the involvement of mMCP-1 in the regulation of the epithelial permeability by proteolysis of tight junction proteins. These observations were supported by egg counting studies showing that in infected mMCP-1-KO's the schistosome eggs were largely maintained in the intestinal wall, whereas in infected WT animals an increased egg expulsion in the gut lumen was noted as measured by an increased faecal egg load.
In conclusion, this study strongly suggests that the bone marrow does respond to infection resulting in a defining effect on parasite expulsion. In addition, these results clearly demonstrate that mMCP-1, a protease released by the recruited MMC in the inflamed ileum, is involved in the destruction of the intercellular epithelial integrity resulting in an increased egg expulsion from the gut wall. *Supported by IUAP P5/20, FWO-grant G.0377.04 and an IWT-grant (SB1146 to FDJ)*

- B 15 -

REGIONAL DIFFERENCES IN GASTROINTESTINAL MOTILITY DISTURBANCES DURING ACUTE NECROTISING PANCREATITIS. T. Seerden (1), B. De Winter (1), A. Herman (2), P. Pelckmans (1), J. De Man (1). (1) University of Antwerp - Division of Gastroenterology ; (2) University of Antwerp - Laboratory of Pharmacology.

Background : Patients with acute pancreatitis often suffer from an impaired gut function but the mechanism of this dysfunction is unclear. We studied the effect of acute necrotising pancreatitis (ANP) on in vivo motility and in vitro contractility in mice.
Methods : ANP was induced by feeding young female mice a choline-deficient ethionine (0.5 %) supplemented (CDE) diet during 72 hours. The pancreas was histologically scored for ANP according to Van Laethem *et al.* (Gastroenterology 108 ; 1917-22, 1995). We studied gastric emptying and intestinal transit in vivo, 15 min after intragastric gavage of a semiliquid Evans blue meal. In vitro isolated muscle strips were prepared to asses neuromuscular contraction and relaxation of the gastric fundus and small intestine. Results : The pancreas of CDE fed mice showed typical signs of ANP : widespread acinar cell necrosis accompanied by oedema and inflammatory cell infiltrate. Only mice with a histological score e 4 were included. ANP significantly inhibited gastric emptying from 61.2 ± 9.8% to 34.9 ± 7.1 %. In the intestine, the migration of the front of the semiliquid meal and the geometrical centre were significantly inhibited in ANP mice : from 63.4 ± 5.6 % to 32.5 ± 5.4 % for the transit of the distal front and from 2.8 ± 0.2 to 1.6 ± 0.1 for the geometric centre (ne8). In gastric fundus muscle strips from ANP mice, contractions to carbachol (0.01-1µM), excitatory nerve stimulation (0.5-8 Hz) and KCl (50mM) were comparable to controls while contractions to Substance P (1-100 nM) were impaired. Non-adrenergic non-cholinergic relaxations of the gastric fundus to nitric oxide (1-100µM), ATP (30µM) and inhibitory nerve stimulation (1-8 Hz) were not affected in ANP mice. In jejunal muscle strips from ANP mice, contractions to carbachol, Substance P, excitatory nerve stimulation and KCl were significantly impaired compared to the jejunal contractility in control mice (ne8). Jejunal muscle strips did not relax to inhibitory nerve stimulation (1-8 Hz), either in controls and ANP mice.
Conclusion : Our results show that ANP delays gastric emptying in vivo, which is associated with a specific reduction of Substance P contractility in vitro. ANP also impairs intestinal transit in vivo and this is associated with a receptor-independent reduction of intestinal contractility in vitro. These results indicate that ANP impairs gastric and intestinal function but that the mechanisms underlying these dysfunctions show regional differences.

- B 16 -

DETERMINANTS OF PROXIMAL EXTENT OF GASTROESOPHAGEAL REFLUX : VISCOCITY OF REFLUXATE AND ACUTE ESOPHAGITIS. X. Zhang, S. Emerenziani, J. Tack, J. Janssens, D. Sifrim. Center for Gastroenterological Research, K.U.Leuven.

Gastroesophageal reflux with high proximal extent is more frequent in patients with GERD and more often associated with symptoms. Boluses of high viscosity have a slow aboral intraesophageal transit and thickened diets are used to reduce GER in babies. Acute esophagitis increases esophageal tone (Zhang *et al.* 2004). We **aimed** to characterize the role of refluxate's viscosity and increased esophageal tone induced by acute esophagitis in proximal extent of GER.
Methods : We set up an in-vivo feline model to study the proximal extent of GER. Studies were performed on 5 adult cats under ketamine sedation. Reflux events were simulated by fast intraesophageal retrograde injection of a radiopaque solution (1ml) at a fixed flow rate (10ml/sec) using an electronic pump. The retrograde bolus injections were performed at the proximal margin of the LES, via a percutaneous gastrostomy. The animal's body and head were elevated 30o. Digital video imaging of fluoroscopic recordings allowed calculation of velocity and proximal esophageal extent of the injected boluses. Experiments were performed with 3 solutions of increasing viscosity containing 0, 0.5 and 1 % of metilcellulose (MC) before and after acute esophagitis (0.1N HCl intraluminal perfusion, 80min).
Results : Retrograde injections of the most viscous solution (1 %MC) had a lower proximal extent and reached the proximal esophagus significantly slower than less viscous solutions (0-0.5 %MC). Esophagitis promoted higher proximal extent of the most viscous solution.
Conclusion : Proximal extent of reflux results from a balance between gastric, sphincteric and esophageal factors. Physical properties of the refluxate and anatomical factors may affect proximal extent of reflux in opposite directions. On one hand reflux of a more viscous material in the subcardial region may have lower proximal extent and produce slower proximal esophageal distension. On the other hand, increased esophageal tone, with acute esophagitis, may favour a high proximal extent of reflux. Healing esophagitis and thickening diets may reduce proximal extent of postprandial reflux.

	Proximal extent (cm)		Velocity (cm/sec)	
	without esophagitis	With esophagitis	without esophagitis	With esophagitis
0.0 %MC	6.7 ± 0.2	6.8 ± 0.5	8.2 ± 2.3	6.9 ± 2.1
0.5 %MC	6.4 ± 0.5	6.3 ± 0.4	4.1 ± 1.5	2.6 ± 0.5
1.0 %MC	4.8 ± 0.4 *	5.7 ± 0.4 #	1.7 ± 0.6 *	2.2 ± 0.4

* one-way ANOVA, vs 0.0 % & 0.5 % MC, $p < 0.05$
# paired t test, vs "without esophagitis", $p < 0.05$

-C01-

PREVALENCE OF H. PYLORI-RESISTANCE TO ANTIMICROBIAL IN BELGIUM : LAST DATA FROM A PROSPECTIVE SURVEILLANCE PROGRAM IN 3 DIFFERENT CENTRES IN BELGIUM. A. Burette (1), Ch. VandenBorre (2), C. Berhin (3), H. Nizet (3), Y. Glupczynski (3), (1) Gastroenterology Unit, CHIREC/sites de la Basilique & E. Cavell, (2) Microbiology Dept, CHU Brugmann, Brussels, (3) Microbiology Dept, Cliniques Universitaires U.C.L. Mont-Godinne Belgium.

Aim of the study : The main determinants of anti-H. pylori (Hp) treatment success are patient compliance and the antimicrobial susceptibility of the infecting strains. Since Hp may develop resistance to many of commonly used antibiotics including those of the nitro-imidazoles, macrolides and quinolones groups, awareness of the local and national resistance rates for metronidazole (M), clarithromycin (C) and even ciprofloxacine (Q) is essential to optimise the choices of effective anti-H.pylori treatment strategies. In Belgium, M-resistance is estimated to range from 17 % to 45 % with an average of 30 %, while C-resistance averages about 15 % with ranges from 3-28%. Resistance to tetracycline (T) and amoxicillin (A) were also extremely rare (£1 %). Of note however was the unexpectedly high resistance rate to Q (18%, ranges : 12-33 %) which has been proposed by some authors as part of rescue therapies (A. Burette, Y. Glupzynski, *et al.* : Antimicrobial resistance rates of Hp in Belgium : results of the 2003 national surveillance program, BW 2004). The aim of this study is to follow the local prevalence of primary resistance to M and C in Hp isolates**.**
Method : Adult patients, without history of recent intake of antimicrobials, PPI or Bi salts, attending the out-patients endoscopy clinic were prospectively tested for the presence of Hp-infection. Hp status was assessed in antral and body biopsies by urease test, histology and culture. Systematic susceptibility testing to antimicrobial including M, C and Q (+A and T) was performed by disc diffusion method and/or E-test in all positive isolates. Evaluation of the primary resistance rates to M and C was assessed in all patients who never received previous Hp eradication therapy.
Results : Data presented her concern the 9 or 10 first months of 2004 according to the centres. Respectively 115, 79 and 41 Hp-positive cultures were tested in the NCB, St-Luc and Mont-Godinne Hospitals. The prevalence rates (%) of primary resistance to M, C and Q in Hp isolates are reported in the next table :

AB susceptibility 2004	NCB (n = 115)	St-Luc (n = 79)	Mont-Godinne (n = 41)
MR (%)	23.5	44.9	33.3
CR (%)	15.7	14.1	25.6
MR CR (%)	7.8	5.1	12.8
QR (%)	14.8	14.5	20.0

Conclusion : High rates of primary resistance of Hp strains to M and/or C are observed in three different Belgian centres. Also worrying is the seemingly increasing rates of double C+M-resistant strains over the last years. Large variations in resistance rates by centres do occur, especially to C. A uniformly high rate of Q-resistance is found among Hp strains.
Continuous follow-up of local and national antimicrobial resistance rates is clearly needed because of the high prevalence of resistant or multi-resistant strains (including resistance to fluoroquinolones) which may render the recommended first-line regimens ineffective in a near future. Future multicentre resistance surveys should be planned on a regular basis in order to monitor antimicrobial resistance trends in H. pylori in Belgium.

- C 02 -

EVALUATION OF THE IMMUNOCARD STAT!® HPSA® TEST FOR THE DIAGNOSIS OF H.PYLORI INFECTION BEFORE AND AFTER ERADICATION THERAPY. A. Burette (1), P. Deprez (2), M. Delforge (3), E. DeKoster (4). (1) CHIREC/Nouv. Clin. Basilique/ IME.Cavell, Brussels ; (2) Clin. Univ. St-Luc, UCL, Brussels ; (3) Clin. St-Joseph, Liège ; (4) CHU. Brugmann, VUB, Brussels.

Aim of the study : Testing of *H.pylori* (*Hp)* antigens in stools has shown promising results in adults for the non-invasive diagnosis of gastric infection using commercially available kits. Testing for *Hp* antigens in faeces also has also been proposed for monitoring the success of eradication therapy, although results are contradictory. The Immuno*Card* STAT!® HpSA® (ICS-HpSA), Meridian Bioscience Europe, is a new rapid in vitro qualitative in-office procedure for the detection of *Hp* antigens in human stools. It has been proposed as a non-invasive test for the diagnosis of *Hp* infection before or after treatment by demonstrating the persistence or the loss of *Hp* stool antigen following therapy. ICS-HpSA is a rapid lateral flow immunoassay that utilizes a monoclonal anti-*Hp* antibody as the capture and detector antibodies. The aim of this study was to evaluate the ICS-HpSA in the primary diagnosis of *Hp* infection and to study the test performance after eradication therapy.

Method : This multicentre study included dyspeptic patients attending the out-patients endoscopy clinic. At endoscopy biopsy specimens from the antrum and the corpus were obtained for rapid urease test (RUT), culture and histology. The reference standard for *Hp*+ve patients was defined as a positive culture alone or a combination of a positive histology and positive RUT or Urea breath test (UBT). Patients with < 2 positive test (except for culture) were considered negative. In the post-treatment evaluation, the reference standard for *Hp*+ve patients was defined as before treatment (in case of control endoscopy) or as a positive C^{13}UBT alone. In case of discordance between the ICS-HpSA and the UBT a second control, either by UBT or OGD+B, 2-3 month later was recommended to confirm the first results (the patient being considered infected or cured according to the positive or negative result of the control test). Post-treatment were carried out e4-12 weeks after eradication therapy and all test were performed in patients having not received any antibiotic (whatever the reason), bismuth, anti-H2 or PPI-based therapy within the last 2 weeks.
Results : To date 137 patients were evaluated, 84 before therapy and 53 after eradication therapy. 5 tests were equivocal (3 before and 2 after treatment). Sensitivity, specificity, PPV and NPV of the ICS-HpSA in the primary diagnosis of Hp infection were 85.5 %, 88.9 %, 94.0 %, 77.4 % with positive and negative likelihood ratios of 7.70 & 0.16 respectively and accuracy of 83.5 %. Similar figures for the post-treatment evaluation were 78.6 %, 85 %, 73.3 %, 91.9 %, 5.24 & 0.25 and accuracy of 83.3 %.
Conclusion : In our experience, the ICS-HpSA monoclonal antibody-based stool antigen test, although performant, is less accurate than the combination of biopsy-based diagnostic tests or UBT either before or after therapy. It is quite simpler to perform and cheaper than the UBT. However, patients may be reluctant to collect stool specimens (20-30 % in our experience). Additional studies evaluating the accuracy of stool antigen testing for both initial diagnosis and post treatment follow-up are required before definitive recommendations can be considered.

Acknowlegement : Meridian Bioscience Europe kindly provided the ImmunoCard STAT!® HpSA®

- C03 -

HELICOBACTER PYLORI STOOL ANTIGEN FOR THE DETECTION OF H PYLORI INFECTION IN CHILDREN : DETECTION OF H PYLORI STOOL ANTIGENS IN CHILDREN WITH MONOCLONAL ANTOIBODIES. A. Salamé, A. Sengier, S. Cadranel. Department of Gastroenterology, HUDERF-ULB.

The 13C-urea breath test (UBT) is commonly used as a non-invasive screening method for the detection of HP infection in children as well as a "gold standard" test to assess the efficacy of treatment. Detection of HP stool antigens (HPSA) using polyclonal antibodies is also available but less accurate.
Aim : evaluation of a new monoclonal HPSA test in HP infected children.
Methods : monoclonal HPSA was performed in 20 children (group 1) and results compared to endoscopic, histologic (HP gastritis) and microbiologic (HP culture) findings. In 7 children (group 2), the efficacy of an eradication treatment for HP infection was assessed by means of a 13CUBT and compared to monoclonal HPSA.
Results : in group 1, HPSA results were in agreement with endoscopic findings in 15 children with HP infection and in 3 non infected children. However HPSA was negative in 2 children with HP infection detected by histology and culture. In group 2, a complete concordance between 13CUBT and HPSA was observed in 5 children successfully treated and in 2 children with persistent infection.
Conclusion : Although less sensitive than the 13CUBT, monoclonal HPSA is a valuable, easy, quick and unexpensive non-invasive tool for the detection and follow up of HP infection in children. The only real draw-back results in the difficulty to obtain patient's stools.

- C 04 -

HELICOBACTER PYLORI, A BUG INVOLVED IN THE DEVELOPMENT OF GASTRIC LYMPHOMA. Dr. A. Driessen, Dept of Pathology, University Hospital Maastricht, The Netherlands.

The development of a gastric marginal zone cell lymphoma or mucosa-associated lymphoid tissue (MALT) lymphoma is a multistage process, in which a Helicobacter pylori-associated gastritis is the primary step of this process. H. pylori causes an inflammation of the mucosa with development of MALT, from which this low grade malignancy arises. The etiopathological role of H. pylori in the histogenesis of marginal zone cell lymphomas is demonstrated by several retrospective studies, reporting a regression of this neoplastic process after eradication of H. pylori in 60-90 % of cases. Recently, this success story was confirmed in a large prospective multicenter study. Elimination of a tumour by an antibiotic treatment challenges however the concept of a neoplastic process which in principle grows independently of environmental stimuli. Molecular analysis has shown that several molecular events occur during this multistage process, of which t(11 :18) (q21 :q21), t(1 ;14) (p22 ;q32) and, the more recently discovered translocation, t(14 ;18) (q32 ;q21) are the common cytogenetic abnormalities. These cytogenetic abnormalities, such as t(11 :18) (q21 :q21) determine the point of no return, in which the tumour fails to regress after antibiotic treatment. Moreover despite the high success rate of eradication therapy long term follow-up is necessary as relapses may occur even after years. In case of treatment failure or in case of H. pylori negative gastric lymphomas other treatment options should be considered such as chemoradiotherapy. In spite of its low grade malignancy marginal zone cell lymphomas may disseminate to lymph nodes or may transform into a diffuse large B-cell lymphoma, a high grade malignancy.

INVITED LECTURE

- C 05 -

THE CLINICAL EVALUATION OF GASTRIC CANCER RISK : BEYOND DETECTION AND ERADICATION OF H. PYLORI. Robert M. Genta, Geneva, Switzerland

Gastric cancer remains a frequent lethal malignancy worldwide. While reducing its incidence is a public health priority in many high-risk countries, assessing the risk of individual patients is an unsolved clinical problem. Chronic gastritis is epidemiologically, biologically and pathologically linked to the development of gastric cancer, and *H. pylori* is listed as a Class I carcinogen. Widespread eradication of *H. pylori* infection is a viable option to decrease the prevalence of chronic gastritis in a population, with the likely effect of reducing the incidence of gastric carcinoma. However, curing *H. pylori* in a patient may not be sufficient to prevent the development of cancer ; other determinants, such as the extension of atrophy and metaplasia, acquire greater weight in influencing the risk, particularly when they are more advanced in their progression. Currently, there are no accepted parameters of risk to predict which patients are be more likely to develop gastric cancer and, therefore, might benefit from surveillance programs. This lecture will discuss a recent proposal for a new reporting system for chronic gastritis based on *staging* and *grading*. While *staging* would convey information on the anatomical extent of the atrophic-metaplastic changes, *grading* would express the cumulative intensity of the inflammatory components. This system could offer gastroenterologists a more immediate perception of the overall condition of the gastric mucosa while also providing useful information about gastric cancer risk.

- C 06 -

MOLECULAR MARKERS OF RESPONSE AND SURVIVAL AFTER FLUOROURACIL BASED CHEMOTHERAPY FOR STAGE II AND III COLORECTAL CANCER. PRELIMINARY RESULTS ON PATIENTS THE GRECCR-01 STUDY. G. Demolin (1), O. Plomteux (1), H. Charlier (1), J. Bury (2), C. Focan (3). (1) Laboratoire de Biologie Moléculaire, Service de Gastroentérologie et d'Oncologie Médicale, CHC Liège (2) Service d'Oncologie Médicale, CHH, Huy ; (3)Service d'Oncologie Médicale, CHC Liège.

Background and aims : Adjuvant chemotherapy improves survival among some patients with stage II and III colorectal cancer. Identifying molecular marker that could be used to select patients susceptible to benefit from that chemotherapy would be useful.
Materiel and methods : We evaluated microsatellite instability (MSI) and polymorphisms in genes that may play a significant role in 5FU metabolism as molecular marker of response to chemotherapy and of survival. We analyzed normal and tumor tissues from 198 patients with stage II and III colorectal cancer who had been treated with an adjuvant 5FU based chemotherapy in GRECCR-01study (Focan, Anticancer Res. 2000 ; 20, 4665-72).
Results : High levels of microsatellite instability (MSI-high) were found in 18 of 88 tumors (20 %). Ten year overall survival for patients exhibiting MSI-high tumors (100 %) was excellent and significantly better than for patients with microstaellite stable tumors (64 %) ($p = 0.01$). However ten years relapse free survival was not statistically different between patients with microsatellite unstable (72 %) and microsatellite stable tumors (67 %), probably due to methodological bias in the design of the GRECCR study. Thymidilate synthase (TS)-3'-untranslated region polymorphism (3' UTR) showed three different genotypes : 6pb/6pb (69 patients) (56.5 %), 0pb/0pb (14 patients) (11.5 %) and 6pb/0pb (39 patients) (32 %). As recently shown by Stoehlmacher in refractory metastatic disease (Br J Cancer. 2004 ; 91 : 344-54), the 6pb/6pb genotype was associated with a better prognosis : ten years relapse free survival was better for the 6pb/6pb genotype (68 %) than for the two others genotypes (51 %) ($p = 0.04$).
Conclusions : Our study confirms that patients with stage II or III colorectal cancer who exhibits high levels of microsatellite instability and who benefits from a 5FU based adjuvant chemotherapy have an excellent prognosis, better than those with microsatellite stable tumors. Moreover, our conclusions regarding TS-3'-untranslated region polymorphism predictive role tends to confirm, in adjuvant situation, the recent data from Stoehlmacher and require further independent prospective evaluation.

Acknowledgements : to surgeons, clinicians and pathologists from participating centers.

- C 07 -

DOES CHRONIC HEPATITIS C VIRUS INFECTION INFLUENCE THE MANAGEMENT OF CANCER PATIENTS RECEIVING CHEMOTHERAPY ? R. Marechal, T. Delaunoit, P. Eisendrath, S. Debroux, A. Awada, H. Bleiberg, A. Hendlisz. Institut Jules Bordet, Belgique.

Background : Hepatitis C infection is a potential source of complications in patients with cancer treated with immunosuppressive chemotherapy. The aim of this study was to evaluate the clinical impact of chronic HCV infection in the management of pts treated with antineoplastic chemotherapy.
Materials and Methods : Between January 1991 and December 2001, patients with chronic HCV infection concomitantly suffering from either haematological or solid cancers, and treated with antineoplastic chemotherapy, were retrospectively reviewed. To determine the incidence and importance of hepatic complications following anti-cancer treatments, patients were assessed based on clinical, biological and radiological evaluation.
Results : Fifty-seven chronic HCV patients (pts) were treated with anti-cancer chemotherapy. Pts characteristics : male/female : 17/40 ; median age 50 years (range 29-85), solid cancers : n = 43 ; haematological cancers : n = 14. Among these, 16 pts (solid / haematological cancers : n = 12/4) developed alterations in liver tests either during or after discontinuation of chemotherapy. Abnormalities were classified in 3 groups following the importance of aminotransferases elevation. Mild alterations were defined as values above 2-times upper normal value (UNV) and below 4-times UNV, moderate alterations as values e 4-times UNV and d 10-times UNV and severe alterations as values > 10-times UNV. These alterations were not clinically significant and did never cause anticancer treatment discontinuation or modifications.
Conclusions : Administration of chemotherapy in patients suffering from chronic HCV infection leads to 28% increase of liver tests. Any significant liver clinical complication was noticed. Consequently we suggest no different clinical management or distinct follow-up for HCV RNA positive patients. Serum aminotransferases level should however be checked in routine biological testing.

Liver tests alteration	Solid cancers (n = 43)		Haematological cancers (n = 14)	
Mild	2 (5%)	2 (5%)	2 (14%)	0 (0%)
Moderate	5 (12%)	2 (5%)	0 (0%)	2 (14%)
Severe	0 (0%)	1 (2,5%)	0 (0%)	0 (0%)
	After chemotherapy	During chemotherapy	During chemotherapy	After chemotherapy

CLINICOPATHOLOGIC ANALYSIS OF APPENDICEAL TUMORS FROM 1,237 APPENDICECTOMIES. V. Tchana-Sato (1), S. Laurent (1), A. Thiry (2), O. Detry (1), M. Polus (1), A. De Roover (1), E. Hamoir (1), B. Detroz (1), S. Maweja (1), T. Defechereux (1), M. Meurisse (1), P. Honoré (1). (1) Dpt of Abdominal Surgery ; (2) Dpt of Pathology, University of Liège, CHU Sart Tilman B35, B4000 Liège.

Background : Malignancies of the appendix are a diverse group of gastro-intestinal tumours rarely suspected before surgery. To help define an appropriate management of appendiceal tumours, a retrospective analysis was undertaken to describe their clinicopathologic behaviour and the literature was reviewed concerning the management of the different types of appendiceal tumours. METHODS : A retrospective review of 1,237 appendectomies performed in our single centre from January 2000 to May 2004 searched for primary appendiceal tumours. Analysis of clinical presentation, histopathology, operation and outcome is presented.
Results : Among 1,237 appendectomies, 11(0.89 %) appendiceal tumours were identified : 5 carcinoïds (0.4 %), 2 adenocarcinoïds (0.16 %), 3 mucinous cystadenomas (0.24 %), 1 adenocarcinoma (0.08%). Acute appendicitis was the most common presentation particularly for carcinoïds and adenocarcinoïds. The majority of the patients underwent appendectomy. One patient in the carcinoïd group was reoperated to complete the excision of mesoappendix. A right hemicolectomy was performed on the two patients with adenocarcinoïd after anatomopathology results were known. Finally, the patient with adenocarcinoma and peritoneal carcinomatosis was treated by cytoreductive surgery plus perioperative intraperitoneal chemotherapy. One patient underwent systemic adjuvant chemotherapy. All patients are alive and disease-free at last follow-up.
Conclusion : Appendiceal tumours are uncommon and most often present as appendicitis. They can be managed by simple appendectomy except adenocarcinomas, adenocarcinoïd and carcinoïds larger than 2 cm, which are most appropriately managed by right hemicolectomy. It is important to mention that all types of appendiceal tumours have a high incidence of synchronous and metachronous colorectal cancer.

- D01 -

INDUCTION OF SEVERE INSULIN RESISTANCE AND HEPATIC COMPLICATIONS COMPATIBLE WITH NASH IN MICE FED A WESTERN-TYPE DIET. C. Dewever, Y. Horsmans, I. Leclercq. Gastroenterology Unit, UCL.

Insulin resistance is a major factor implicated in the pathogenesis of nonalcoholic steatohepatitis (NASH). **Our aim** was to evaluate the effects of high-glucose and/or high-saturated fat/cholesterol diet on emergence of insulin resistance and liver pathology.
Methods : Male C57BL6/J mice were fed ad libitum for 5 weeks a standard chow (CT group, n = 4), a standard chow with high-glucose in drinking water (glucose group, n = 6) or a diet enriched in saturated fat and cholesterol together with high-glucose in drinking water (SFA group, n = 6). Intraperitoneal glucose tolerance and insulin resistance tests were performed in vivo. At the end of the experimental period, blood and tissue samples were obtained for analyses.
Results : Compared with CT, mice from glucose and SFA groups exhibited hyperglycemia (145 ± 5 and 177 ± 8 *versus* 124 ± 2 mg/dL, both $p < 0.001$) and hyperinsulinemia (25.8 ± 4.7 and 30.3 ± 1.6 *versus* 2.8 ± 0.1 ng/mL, both $p < 0.001$). As assessed *in vivo*, mice of glucose group and, to a greater extend, mice of SFA group had glucose intolerance ($p = 0.004$ and $p < 0.001$, respectively) and insulin resistance ($p = 0.007$ and $p = < 0.001$ respectively), which was confirmed by a significant ($p < 0.001$) rise in the HOMA-IR index (0.3 ± 0.1, 3.3 ± 0.6 and 4.7 ± 0.3 in CT, glucose and SFA, respectively). Liver histology appeared normal in mice from CT and glucose groups, but mice in SFA group developed significant macrovesicular steatosis, hepatocyte ballooning and apoptosis and variable panlobular inflammation. Consistently, intrahepatic lipids were significantly increased in SFA *versus* CT (9.0 ± 4.7 *versus* 1.8 ± 0.5 mg lipid/100 mg liver, $p = 0.02$). Importantly, steatohepatitis in SFA mice was associated with a significant up-regulation of collagen Ia1 mRNA expression (1.7 ± 0.4 *versus* 1.0 ± 0.2 in CT, $p = 0.01$).
Conclusions : A diet enriched in glucose, saturated fatty acids and cholesterol induced a severe and prolonged insulin resistance in mice. This was associated with hepatic damage, including activation of fibrogenesis, compatible with NASH. We believe that this original mouse model will be useful to analyse the role of insulin resistance and nutritional factors in the pathogenesis of NASH and for evaluation of treatment.

- D02 -

ELEVATED HEPATIC VENOUS PRESSURE GRADIENT AND HEPATIC ARTERIAL HYPORESPONSIVENESS RELATED TO STEATOSIS IN METHIONINE-CHOLINE DEFICIENT DIET FED RATS. S. Francque (1), P. Pelckmans (1), A. Herman (2), E. Van Marck (3), P. Michielsen (1). (1) Laboratory of gastroenterology, Antwerp University, Antwerp, Belgium ; (2) Laboratory of pharmacology, Antwerp University, Antwerp, Belgium ; (3) Laboratory of pathology, Antwerp University, Antwerp, Belgium.

Background : Changes in splanchnic haemodynamics related to portal hypertension in cirrhosis are extensively studied. Arterial hyporesponsiveness has been demonstrated in the splanchnic and systemic circulation. Hepatic steatosis is evenso associated with haemodynamic changes, especially by reduction in portal venous flow, but these changes are poorly characterised.
Aims : Investigating wether steatosis causes portal hypertension and alterations in vascular responsiveness in a rat model of non-alcoholic steatohepatitis.
Material and methods : 12 male Wistar rats were fed a choline-methionine (MC) deficient diet (6) or a control diet (6) for 4 weeks. After induction of anesthaesia a catheter was inserted in the jugular vein and in the ileocolic vein to measure the hepatic venous pressure gradient. After sacrificing the rat, liver and spleen were removed and weighed. Biopsy samples of both liver lobes were taken. Abdominal and thoracic aortic rings were mounted in organ chambers filled with Krebs solution at 37°C and with continuous oxygenation. Dose-response curves to phenylephrine, after pre-contraction with potassium, were determined. Preservation of endothelial function was checked with acetylcholine, and dose-response curves to acetylcholine were also determined. Student t-test and non-linear best fit (SPSS 12.0) were used where appropriate.
Results : Biopsy confirmed the presence of severe steatosis in the MC diet-fed rats. Their liver/body weight ratio was significantly increased (4.71 ± 0.24 g vs 2.42 ± 0.18 g, p = 0.0001). The spleen/body weight ratio was not statistically different. The venous pressure gradient was higher in the MC diet-fed rats (10-11 mm Hg vs 1-3 mm Hg). The maximal contraction (expressed as % of potassium induced pre-contraction) was significantly lower in the MC diet group (120.4 %, 95 % CI : 116-124.7 %, vs. 151.9 %, 95 % CI : 144.9-159.0 % ; p = 0,008), as was the EC 50 (logEC50 -8.55, 95 %CI : -9.51/-7.58 vs -7.20, 95 %CI : -7.36/-7.034 ; p = 0,032). No significant differences were demonstrated for the thoracic aorta.
Conclusions : In this animal model steatosis is associated with a significant raise in hepatic venous pressure gradient and hence with a certain degree of portal hypertension, and this is also associated with an arterial hyporesponsivenss in the abdominal but not in the thoracic aorta. The underlying mechanisms need to be elucidated.

- D03 -

HEPATIC AND SYSTEMIC HEMODYNAMICS IN PRIMARY PREVENTION OF VARICEAL BLEEDING : A RANDOMIZED STUDY OF VALSARTAN VERSUS PROPRANOLOL IN CIRRHOTIC PATIENTS. S. Evrard, J. Deviere, C. Matos, E. Coppens, C. Keyser, O. Le Moine. Erasme Hospital Brussels.

The current gold-standard pharmalogical treatment for primary prevention of variceal bleeding is propranolol. The potential use of angiotensin II receptor antagonists is still under debate.
Aims of the study : To randomly compare the hepatic and systemic hemodynamic effects of valsartan with propranolol in cirrhotic patients who have never bled from varices. Usual invasive methods as transjugular hepatic and systemic measurements and non invasive procedures of portal hemodynamics with Doppler ultrasonography (US) and Magnetic Resonance imaging (MRI) were compared.
Methods : 17 cirrhotic patients with oesophageal varices grade 2 who had never bled were randomized to receive either propranolol : group A (n = 7, 160 mg/day) or valsartan : group B (n = 10, 40-80 mg/day). All patients underwent laboratory, hepatic and systemic hemodynamic measurements, portal vein US Doppler and MRI assessment before and after 8 weeks of treatment.
Results : The two groups were well matched for clinical, biological, portal, systemic hemodynamics, and radiological parameters. In group A, a significant decrease of HVPG ($p = 0.041$), heart rate ($p = 0.018$), cardiac outpout ($p = 0.018$) and Doppler US portal vein velocity ($p = 0.034$) was observed after 8 weeks of treatment, whereas no significant changes in these parameters were observed for group B (wilcoxon, NP test). No significant changes were observed in both groups for MRI measurements.
Conclusion : This study does not support the portal hypotensive effect of valsartan in primary prevention of variceal bleeding. As far as non invasive measurements of portal hypertension are considered, US Doppler assessment of portal vein velocity correlates with HVPG measurements and MRI as still to prove its efficacy in this setting.

- D04 -

NON-HEART-BEATING DONORS (NHBD) PROVIDE AN ADDITIONAL SOURCE OF ORGANS FOR LIVER TRANSPLANTATION (LT) PROVIDING THAT THE PERIOD OF WARM ISCHEMIA (WI) IS KEPT SHORT. D. Monbaliu (1), T. Roskams (2), J. Greenwood (3), J. Fevery (4), T. Crabbé (4), C. Verwaest (6), J. van Pelt (4), J. Pirenne (1). (1)Abdominal Transplant Surgery, University Hospitals Leuven ; (2)Pathology, University Hospitals Leuven ; (3) Clinical Biochemistry, Oxford, UK ; (4)Hepatology, University Hospitals Leuven ; (6) Intensive Care, University Hospitals Leuven.

Non-heart-beating donors (NHBD) could decrease the gap between available and required organs for liver transplantation (LT). Contrary to kidneys, the use of NHBD livers remains scarce because these grafts exposed to Warm Ischemia (WI) suffer from a higher rate of Primary-Non-Function (PNF). The maximal period of WI that liver grafts tolerate and the mechanisms of WI injury are not known with certainty.
Aim To study this, we developed a reproducible-clinically relevant large animal model of NHBD LT and we analyzed the influence of WI on survival, graft function, functional, biochemical, and histological parameters post LT.
Methods Porcine livers were submitted to increasing periods of WI (0, 15, 30, 45 and 60min), flushed *in situ*, retrieved and transplanted after 4 hrs cold-storage. PNF and day 4 survival were recorded. Blood and liver samples were collected before and after LT. Circulating Aspartate Transaminase (AST), and factor V, bile production, endothelial function [clearance of Hyaluronic Acid (HA)], Kupffer cell activation (Beta-galactosidase), and Tumor Necrosis Factor (TNF)-± and Interleukin (IL)-6 production were monitored post LT.
Results PNF developed in 100 % after 60minWI, 50 % after 30and 45minWI and was absent after 0 and 15min WI. Day 4 survival was 100 % in 0min WI, 83 % in 15min WI, 33 % in 30 and 45min WI, and 0 % in 60min WI. A correlation was seen between WI and peak AST. Bile production was reduced, proportional to WI duration. Factor V levels were inferior in groups exposed to > 30min WI. HA clearance recovered more rapidly in groups with less WI but remained impaired in PNF recipients. Beta-galactosidase raised, proportional to WI duration. TNF- ± and IL-6 were higher in PNF *vs.* non-PNF recipients. In PNF recipients, panlobular mediovesicular hepatocellular vacuolization was a prominent histological feature already seen immediately after exposure to > 30min WI (e.g. before cold storage / reperfusion). Minor histological changes seen after shorter periods of WI and in non-PNF recipients were reversible after reperfusion whereas hemorrhagic necrosis developed in all PNF recipients.
Conclusions : The time-window for the safe use of NHBD livers is short : < 30min WI. After 30-to-45min WI, the risk of PNF rises to 50 % and livers submitted to 60min WI are not viable. Hepatocellular damage is caused by WI *directly*, but is also *secondarily* aggravated after reperfusion via endothelial dysfunction and inflammation presumably orchestrated by Kupffer cell activation and TNF-a release. These data provide(i) new insight into the tolerance of liver to WI and the mechanisms of WI injury ; and (ii) new guidelines to be used clinically. Since 2003, Belgian LT centers started to use NHBD livers and of 212 LT done in 2003, 7 (3.3 %) were with NHBD grafts exposed to short WI, and this with a favorable outcome.

- D05 -

MACHINE PERFUSION OF MARGINAL HUMAN LIVERS : HEMODYNAMICS, METABOLISM AND MORPHOLOGY. D. Monbaliu (1), T. Roskams (1), T. Crabbé (1), R. De Vos (1), J. Brassil (2), D. Cassiman (1), D. Schein (1), J. Fevery (1), J. Pirenne (1). (1) University Hospitals Leuven, Leuven, Belgium ; (2) Organ Recovery Systems, Des Plaines, USA.

Wider use of 'marginal' or "Expanded" Donors (ED) could increase the number of livers for transplantation (LTx) but this strategy is limited by the absence of techniques to optimize preservation and to predict liver graft viability before Tx (in order to avoid primary graft non function). In renal Tx, Machine Perfusion (MP) allows to assess graft quality, optimizes preservation and this results in improved outcome after Tx. Whether this technology (and its benefits) apply to marginal livers is not known.
Aim. To study : 1) the feasibility of MP of ED human livers ; 2) the hemodynamics & biochemical behavior of these MP livers ; and 3) their morphology.
Method. 9 discarded livers (5 > 50 % steatosis ; 4 other reasons) were perfused (after 11hrs 50' cold storage) via Hepatic Artery (HA) and Portal Vein (PV) with 4-6ºC non-oxygenated Belzer Machine Perfusion Solution during 24hrs using a liver MP prototype (Organ Recovery Systems). HA was connected to an unlimited flow, pressure-controlled (25/30 mmHg) system and PV to a flow-limited (< 600ml/min), pressure-controlled (< 7 mmHg) system. HA and PV Vascular Resistance (VR) were monitored. Transaminases (AST), PO2, PCO2, pH, lactate, and glucose were measured in the circuit. Biopsies were taken before and after MP for standard (n : 9) & Electron Microscopy (EM) (n : 2).
Results : HAVR was constantly higher (0.24-1.12 mmHg.min/ml) than PVVR (0.04-0.12 mmHg.min/ml). Immediate HA&PVVR were high and decreased gradually during MP. There was a progressive release of AST during MP. Of note, AST release from steatotic livers was higher *vs* non-steatotic livers : (6825 vs 924U/l, p = 0.007). Initial pO2 (154.3-238 mmHg) decreased rapidly after 10' MP (20.1-48.2 mmHg) and remained low thereafter. Initial pCO2 (2.2-2.5 mmHg) increased first sharply after 10' (19-22.3 mmHg) and slowly thereafter (19.8-33.9 mmHg at 24 hrs). Initial pH (7.300-7.340) decreased first rapidly after 10' (6.841-6.963) and slowly thereafter (6.263-6.522). Lactate was elevated (11.9-19.9 mmol/l) after 24hrs MP. Glucose was released in the circuit (140-168 at start, and 666-1118 mg/dl at end of MP). Bile was produced during MP (40-120 ml/24hr). Histology revealed adequate preservation of lobular architecture and parenchyma after MP. EM showed well-preserved cellular ultrastructure and minimal ischemic injury.
Conclusion. MP of marginal livers is shown -for the first time- to be feasible. VR progressively decreases during MP, indicating a better penetration of the microcirculation and possibly better preservation, similar to MP kidneys. Transaminase release is documented during MP, particularly in severely steatotic livers. All livers tested -albeit marginal- display unequivocal signs of aerobic and anaerobic metabolism, produce bile, and are morphologically well-preserved by MP. MP offers promising possibilities to better preserve and assess marginal livers before Tx.

- D06 -

INDUCTION OF TOLERANCE BY MYELOCONDITIONNING AND DONOR STEM CELLS INFUSION IN LIVING DONOR TRANSPLANTATION : A PILOT STUDY. V. Donckier (1), R. Troisi (2), S. Ricciardi (2), I. Colle (2), H. Van Vlierberghe (2), M. Toungouz (1), L. Noens (2), A. Le Moine (1), M. Libin (1), B. de Hemptinne (2), M. Goldman (1). (1) Hôpital Erasme, ULB, Brussels ; (2) UZ Gent, Gent.

Background and aim of the study : Induction of transplantation tolerance, defined as survival of a functioning allograft in absence of continuing immunosuppression (IS), would be a major progress. We investigated a protocol to induce tolerance to living liver graft using non-myeloablative conditioning and donor stem cells (SC) infusion, in patients with advanced liver cancers.
Patients and methods : Five patients with intra-hepatic cancers, outside from the criteria for liver transplantation (LT) (multifocal hepatocellular carcinoma in patients 1, 3 and 5 and hylar cholangiocarcinoma in patient 2 and 4), were included. In patients 1 and 2, preparative regimen, cyclophosphamide and anti-thymocyte globulin (ATG), and purified donor CD34+ SC were given prior to LT. Living donor liver transplantation (LDLT), using right lobe, was performed after hematological reconstitution, respectively 40 and 55 days after SC infusion. Posttransplant IS consisted in tacrolimus or rapamycin monotherapies in patient 1and 2 respectively. In the next cases, (patients 3, 4 and 5) conditionning was performed immediately after LDLT (day 0), using ATG (days 1 to 5) and rapamycin. Donor $CD34^+$ SC were given on day 7 after LDLT, and IS stopped when liver tests returned to normal.
Results : The entire procedures could be completed in the 5 cases. No GVH was observed after donor SC infusion. A transient macrochimerism was observed only in patient 1. IS was stopped, respectively 90, 28, 18, 10 and 23 days post LDLT. Patients 3 and 4 developped subsequent acute rejection, rapidely reversible in patient 3, but requiring maintenance IS in patient 4. In all the patients, posttransplant mixed lymphocyte cultures showed donor specific hyporesponsiveness as expressed by decreased proliferation and reduced production of IL2 and IFNg against donor antigens as compared with pretreatment levels, in a context of global immunodeficiency, as indicated by low responses against 3th party antigens. The first patient died from tumor recurrence 370 days after LT. The second patient is alive, 510 days after LDLT, with a tumor recurrence. The 3 others are alive and disease-free, respectively 210, 70 and 55 days after LDLT.
Conclusion : Non myeloablative conditionning and donor SC infusion was able to induce donor-specific operational tolerance to liver allograft in 4/5 of our patients, without prohibitive related-morbidity. These early results will prompt us to propose such approach for patients within the classical criteria for LT, in whom living donor is available.

INVITED LECTURE
MARC HAUTEKEETE LECTURE

- D07 -

CLINICAL ASPECTS OF BILIRUBIN DETERMINATION. Johan Fevery (KUL Leuven)

The metabolisation of bilirubin, an endogenous compound, can serve as an example for modifications of a large series of other substances and pharmaca. The major steps in the metabolism of bilirubin are production from hemoglobin, conjugation with UDP-sugars and biliary secretion. In the intestine, a small part can undergo enterohepatic circulation, while the major part undergoes breakdown by bacterial enzymes. Serum levels of unconjugated (UCB) and conjugated biliruibn can testify for hemolysis, decreased conjugation or diminished biliary secretion. Most of the bilirubin is bound to albumin : for the unconjugated species, this is very pronounced with a free fraction of < 10*9 µM and a strong binding affinity, for the conjugated fraction, the binding is less strong and a small fraction undergoes glomerular filtration (and filtration in the MARS system). Increased levels of UCB in bile lead to pigment gallstones. UCB is potentially toxic for brain tissue, but small amounts are advantageous, since it is a strong anti-oxidant. As such, it has recently been shown that individuals with higher UCB (Gilbert syndrome) are protected against cardiovascular disease. The fate in the intestine explains fasting hyperbilirubinaemia and the formation of pigment gallstones in Crohn's disease. Molecular biology has documented the gene mutations of the conjugating enzyme. Several transport proteins have also been identified in the hepatocyte. They are abnormal in several congenital disorders of cholestasis.

- D08 -

GENETIC POLYMORPHISMS IN PRIMARY SCLEROSING CHOLANGITIS (PSC) : A CANDIDATE GENE STUDY. L. Henckaerts, M. Ferrante, T. Hlavaty, M. Pierik, N. Van Schuerbeek, J. Fevery, W. Van Steenbergen, C. Verslype, P. Yap, F. Nevens, P. Rutgeerts, S. Vermeire. University Hospital Gasthuisberg, Department of Gastroenterology.

Background & Aims PSC is a progressive cholestatic disease commonly associated with inflammatory bowel disease (IBD) and characterized by fibrosing inflammatory destruction of intra- and/or extrahepatic biliary ducts. The precise pathogenesis of PSC is unknown, but immunologic, bacterial, viral and toxic factors may play a role in a genetically susceptible host. A number of interesting candidate genes, both from a functional perspective (MMP-3, MMP-9, CCR5) as well as from their chromosomal position (CCR5, CARD15) in a region of linkage for IBD have been reported recently but results have either never been confirmed or are inconclusive.
Methods A total of 67 patients with PSC (36 with concomitant IBD (15 CD/18 UC/3 IC) ; 47 male/20 female) were identified and were genotyped for CCR5-D32, for CARD15 variants A702T, G908A and L1007fsinsC, and for 6 non-synonymous polymorphisms in MMP-9 (A20V, E82K, N127K, D165N, R279Q and R547P). Results were compared to a cohort of 336 IBD patients (213 CD, 123 UC) without PSC and 313 healthy controls. Diagnosis of PSC was based on (1) laboratory findings consistent with chronic cholestasis and (2a) characteristic radiographic appearance or (2b) consistent histologic features on liver biopsy and (3) absence of conditions associated with secondary sclerosing cholangitis.
Results The CCR5-D32 allele frequency in patients with PSC, irrespective of concomitant IBD, was significantly lower (4.1 %) as compared with healthy controls (12.14 %, p = 0.006) and IBD patients without PSC (12.65 %, p = 0.005). For MMP9, all studied SNPs had an allele frequency below 1 %, except for R279Q (32 %), but no significant differences were observed for this SNP in the different groups. The frequency of CARD15 variants in PSC was 24.6 % and was not different from the frequency observed in healthy controls (21.9 %) or UC (16.4 %), but was significantly lower than in CD (44 %, p = 0.006). CARD15 mutation prevalence in PSC patients with IBD (31.3 %) was not different from the control CD group. **Conclusion** We found a significantly lower frequency of the CCR5-D32 mutation in PSC patients compared to IBD patients without PSC and to healthy controls, suggesting a protective effect of the CCR5-D32 variant on PSC, consistent with a role for CCR5 and its ligands in disease pathogenesis. In contrast with previous findings, we did not observe association of PSC and CARD15 or MMP-9 variants.

- D09 -

PEGINTERFERON ALFA-2A (40KD) PLUS RIBAVIRIN IS AS EFFECTIVE IN PATIENTS RELAPSING AFTER CONVENTIONAL INTERFERON BASED THERAPY THAN IN NAÏVE PATIENTS : RESULTS FROM THE BERNAR-1 TRIAL. F. Nevens (1), H. Van Vlierberghe (2), F. D'heygere (3), J. Delwaide (4), M. Adler (5), J. Henrion (6), J. Henry (7), A. Hendlisz (8), P. Michielsen (9), B. Bastens (10), R. Brenard (11), O. Van Der Meeren (12). (1) UZ Gasthuisberg, Leuven ; (2) UZ Gent, Ghent ; (3) AZ Groeninge, Kortrijk ; (4) CHU Liège, Liège ; (5) Cliniques universitaires Erasme, Brussels ; (6) Hôpital de Jolimont, La Louvière ; (7) CHU Charleroi, Charleroi ; (8) Institut Bordet, Brussels ; (9) UZ Antwerpen, Edegem ; (10) CH Saint-Joseph-Espérance, Liège ; (11) Hôpital Saint-Joseph, Gilly ; (12) NV Roche SA, Brussels.

Background : Treatment with peginterferon alfa plus ribavirin (RBV) is standard of care in the initial treatment of chronic hepatitis C (CHC). The Belgian Randomised trial for Naïve and Relapsers (BERNAR-1) investigated the safety and efficacy of this regimen versus a conventional interferon-based combination therapy, and compared naïve patients versus patients who relapsed after initial treatment with conventional interferon with or without ribavirin.
Methods : Study medication consisted of peginterferon alfa-2a (40KD) (PEGASYS) 180 µg qw for 48 weeks, or interferon alfa-2a 6MIU tiw for 12 weeks then 3MIU tiw for 36 weeks (IFN), both combined with RBV (1,000 or 1,200 mg/day) for 48 weeks. Randomisation was stratified according to pretreatment status (treatment-naïve versus relapse) and presence of cirrhosis.
Results : 443 patients were randomised and received at least one dose of study medication (ITT, missing = failure). The baseline parameters were well balanced across treatment arms. The patients were predominantly male (54 %), Caucasian (91 %), older than 40 (68%), with a BMI > 25kg/m2 (50 %) ; 16 % had cirrhosis ; 22 % were relapsers. At baseline, 63 % of patients had genotype 1 infection and 34 % had HCV-RNA > 800,000IU/mL. A significantly higher proportion of patients in the PEGASYS group than in the IFN group had a sustained virological response (SVR) : 52 % vs. 27 %, $p < 0.001$. The proportion of patients with SVR in the naïve population was 54 % (PEGASYS) versus 27 % (IFN) ; in the relapse group, 43 % (PEGASYS) vs. 26 % (IFN). The difference between treatment groups was highly statistically significant in both naïve and relapse populations ($p < 0.001$), while the difference in response rate between naïve and relapsers was not statistically significant ($p = 0.237$).
Conclusions : The CHC population in Belgium shows various factors usually associated with lower response to therapy. Despite this, peginterferon alfa-2a (40KD) plus ribavirin demonstrates efficacy results of 54 % SVR that are consistent with previous reports. In patients relapsing after conventional interferon-based therapy, once-weekly peginterferon alfa-2a (40KD) plus ribavirin provides similar response rate than in naïve patients.

- D10 -

INFLUENCE OF BODY MASS INDEX (BMI) ON THE RESULTS OF DIFFERENT INTERFERON-BASED REGI MENS FOR THE TREATMENT OF CHRONIC HEPATITIS C. H. Aktas, S. Francque, S. Vogels, E. Van den Bogaert, P. A. Pelckmans, P. P. Michielsen. Gastroenterology and Hepatology,University Hospital Antwerp (UZA), Edegem, Belgium.

Introduction : Although the efficacy of antiviral therapy in chronic hepatitis C has improved since standard interferon (IFN) monotherapy was introduced, nonresponse to the current therapies remains common. Several predictive factors have been shown to influence response. Obesity, a modifiable risk factor, may have a negative effect on treatment response to both pegylated and standard IFN monotherapy.
Aims : 1) To describe the characteristics of hepatitis C patients 2) To compare the efficacy of different treatment modalities 3) To identify the independent factors, which influence the sustained virologic response.
Patients and methods : A retrospective review was performed of all patients with chronic hepatitis C at our centre from 1990 to 2004.
Results : Of the 229 patients 133 (58%) were male, with a mean age at diagnosis of 44.0 ± 14.2 y. Genotype (G) distribution was as follows : 58.1 % G 1, 7.2 % G 2, 25.7 % G 3, 7.8% G 4 and 1.3 % G 5. Blood transfusion (30 %) and IV drug use (30 %) were the most important modes of transmission. 152 patients were treated with 242 therapy courses, with complete data for 191 treatments. Sustained virological respons (SVR) rates were l0.4 %, 30.0 %, 24.0 % and 42.1 % for IFN monotherapy, IFN-ribavirin combination therapy. Peg-IFN ± 2b-ribavirin and Peg-IFN ± 2a-ribavirin combination therapy respectively. SVR was significantly better for G 2 and 3 compared to G 1 and 4 ($p = 0.011$). Ethnic origin was also of influence ($p = 0.043$) with a worse SVR in the black race (mainly G 4). Strikinglv, BMI - defined as 3 categories- normal : < 25 kg/m^2, overweight : 25-30 kg/m^2, obesity : > 30 kg/m^2- was a highly significant predictor of SVR ($p = 0.002$) with overall SVR of 37.3 %. 13.6 % and 11.1 % respectively.
Conclusion : The results of the different treatment regimens for chronic hepatitis C at our centre reflect the current experience, with a superior result for the IFN-ribavirin combination therapy. Besides G 1 and black race, a higher BMI is strongly associated with a lower SVR even in the weight-based treatment regimens. As overweight is increasingly common, this factor should be taken into account in tailoring hepatitis C treatment.

- D11 -

IMPROVEMENT OF EUS-GUIDED PANCREATIC FINE-NEEDLE ASPIRATION RESULTS WITH INTRODUCTION OF THE MONOLAYER TECHNIQUE. B. Weynand (1), I. Borbath (2), C. Sempoux (1), C. Galant (1), J. Gigot (3), P. Deprez (2). (1) Service d'anatomo-pathologie ; (2) Service de gastro-entérologie ; (3) Service de chirurgie digestive, Cliniques universitaires St-Luc, Université Catholique de Louvain, avenue Hippocrate, 10, 1200 Bruxelles.

Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) has been performed in our institution for 8 years, mainly focusing on pancreatic lesions. As from mid 2002, the cytology laboratory introduced the monolayer technique (Thermoshandon's Papspin) for cervical smears and by extension to non-gynaecologic specimen.
Aim : to evaluate the impact of monolayer technique introduction on EUS-FNA diagnostic accuracy in pancreatic solid masses.
Methods : retrospective review of all pancreatic FNA performed before (year 2000), during (2002-2003) and after (2003-2004) monolayer technique introduction. Final diagnosis was obtained by surgery or clinical follow-up > 6m and consisted in adenocarcinomas, neuroendocrine tumors, intraductal papillary mucinous tumors (IPMT) and 1 cystic and pseudopapillary tumor. FNA was performed with 22G needles, with no on-site pathologist present.
Results (shown in table) : A significant drop in non-contributory specimens, from the second year of use of the new technique (*, $p < 0.05$). Most of these specimens were neuroendocrine tumors and IPMTs and were due to adequate sampling difficulties. From mid 2003, a significant improvement of sensitivity, accuracy and NPV was observed ($, $$, $p < 0.05$) that compares favourably to published data when on-site pathologist is present. Monolayer technique improved the results by reducing hemorrhagic background, by a better fixation (immediate immersion of material in the fixative), concentration of material by centrifugation and possible ancillary techniques such as immunohistochemistry on cell blocks.

Table	**2000**	**2002-3**	**2003-4**
N	8	98	106
Non-contributive FNA (%)	15	10.9	4.5*
Sensitivity (%)	81	82.5	94.7$
Specificity and PPV (%)	100	100	100
NPV (%)	51	76	88
Accuracy (%)	88	88.7	96$$

Conclusion : the monolayer technique led to a significant improvement of sensitivity, accuracy and NPV in EUS-FNA for pancreatic solid masses, although a learning period was needed both for the cytologist and the endoscopist. These results prove that very accurate results can be obtained without on-site pathologist.

- D12 -

EUS-GUIDED PANCREATICODUODENOSTOMY : A NEW TECHNIQUE FOR MAIN PANCREATIC DUCT DRAINAGE IN ACUTE AND CHRONIC PANCREATITIS. M. Arvanitakis (1), M. Delhaye (1), C. Matos (2), A. Hittelet (1), O. Le Moine (1), J. Deviere (1). (1) Dpt of Gastroenterology, (2) Dpt of Radiology, Erasme University Hospital.

Background : Endoscopic drainage of the main pancreatic duct (MPD) in chronic pancreatitis (CP) can lead to a decrease in pancreatic ductal hypertension, resulting in pain relief. Moreover, MPD drainage can be helpful in acute pancreatitis (AP) complicated with pancreatic duct disruption (PDD), in order to decrease the leakage of pancreatic juice from the viable disconnected pancreatic segment. However, in case of complete MPD obstruction (CP) or complete PDD (AP), transpapillary access to the proximal MPD segment cannot be obtained and conventional endoscopic ductal drainage is not possible. In these cases, a new technique, EUS-guided pancreaticoduodenostomy, can be useful.
Patients and Methods : We report five patients with CP (n = 4) or AP (n = 1) who underwent EUS-guided pancreaticoduodenostomy in order to achieve MPD drainage (mean age : 56 years, range : 47-64). In all patients, cannulation of the proximal segment of the MPD was not possible by means of a transpapillary approach.
Results : Four patients with painful alcoholic CP had mean disease duration of 6 years (range : 3-13) and presented severe ductal dilatation above a tight distal stricture. The remaining patient had presented severe biliary AP, complicated with complete PDR and a pancreaticocutaneous fistula secondary to a previous percutaneous collection drainage. The proximal segment of the MPD was dilated in all patients (mean diameter : 9mm). EUS-guided pancreaticoduodenostomy was performed as follows : Under EUS-guidance, a 19 gauge needle was inserted transduodenally into the proximal, dilated MPD, after its visualization with the tip of the echo-endoscope positioned in the duodenal bulb. Contrast medium was injected, confirming correct location of the needle in the duct. The needle was then exchanged over a guidewire for a 6.5F diathermic sheath, introduced in the pancreaticoduodenal channel using cutting current. This channel was further enlarged by balloon dilation in two patients. Finally, a pancreaticoduodenal plastic straight stent was placed. In both patients who had previous balloon dilation of the pancreaticoduodenostomy, a 10F stent was placed, whereas smaller diameter stents (6F or 7F) were initially used in the remaining patients. These stents were replaced by 10F stents during a second procedure. No complications were recorded. All patients had initial symptom resolution (pain relief and fistula closure) and remained well during a mean follow-up of 10 months (range : 3-30) with the stent in place.
Conclusions : EUS guided pancreaticoduodenostomy is a new method of ductal decompression in patients with CP or AP, in cases when conventional ERCP fails to obtain access to the proximal MPD.

- D13 -

LONG-TERM OUTCOME AFTER ENDOSCOPIC MUCOSAL RESECTION OF SUPERFICIAL OESOPHAGEAL NEOPLASMS. T. Aouattah (1), H. Piessevaux (1), C. Sempoux (2), J. Grodos (2), R. Fiasse (1), Y. Horsmans (1), P. Deprez (1). (1) Digestive Endoscopy Unit, Gastroenterology Dpt, (2) Pathology Dpt, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Ave Hippocrate 10, 1200 Brussels

Several methods of endoscopic ablation of esophageal lesions have been developed for the resection of superficial tumors of the oesophagus. We report a prospective single centre experience using endoscopic mucosal resection with the cap method (EMR-C, Inoue 1993) and compare outcome in low (lesion type I, IIa, IIb d20 mm or IIc d 10mm, stage m or Tis, well or moderately differentiated) versus high risk patients classified pre-operatively according to Ell *et al.* (2000).

Patients and methods : 67 consecutive malignant oesophageal tumors of oesophagus, staged as T1 m1-m^2-sm1-sm^2, N0 by conventional endosonography (radial or linear array echoendoscope EG-3630-UR or EG-3830-UT, connected to a Hitachi EUB6500) and 20 Mhz miniprobes, were treated with EMR-C after submucosal saline injection. APC was performed if necessary for remnant bridges or peripheral islets. 31 patients were classified as low risk group (group 1) and 26 as high risk (group 2). The lesions were spinocellular carcinoma, adenocarcinoma and high grade dysplasia in Barrett's esophagus in 17, 20 and 20 patients, respectively.

Results : 228 EMR-C specimens were removed in 57 patients (mean age 71 y, range 47-88, sex ratio 38M/19F), in 1.3 (1-2) treatment sessions per patient in group 1 and 1.2 sessions (1-3) in group 2, with a mean of 3.3 EMR-C pieces per mucosectomy (1-15). Follow-up was similar in group 1 (16.6 months, 2-47) and 2 (11.5, 2-39). Group 1 significantly differed from group 2 when considering recurrence during follow up (0 % vs 42.7 %, $P < 0.05$), regardless of histological type of tumour. Complications occurred in 0.09 % of sessions and were limited to 6 esophageal strictures requiring 1-3 endoscopic dilatations. During follow-up 3 patients died of various diseases not related to their oesophageal cancer. Seven patients in group 2 were further referred for surgical resection or complementary chemoradiotherapy.

Conclusions : EMR-C is a highly effective and safe method of endoscopic treatment for superficial malignant oesophageal tumours classified as low risk. Outcome after EMR-C depends on proper staging of patients before treatment, but the pathology specimen obtained by EMR also allowed adequate patients' selection for further surgery or radiochemotherapy.

- D14 -

EFFICACY ASSESSMENT OF NATALIZUMAB IN PATIENTS WITH CROHN'S DISEASE : 12-MONTH RESULTS FROM ENACT-2. G. D'Haens (1), JF. Colombel (2), R. Enns (3), BG. Feagan (4), SB. Hanauer (5), I. Lawrance (6), R. Panaccione (7), WJ. Sandborn (8), S. Schreiber (9), S. Targan (10), S. van Deventer (11), P. Rutgeerts (12). (1) Bonheiden, Belgium ; (2) Lille, France ; (3) Vancouver, Canada ; (4) London, Canada ; (5) Chicago, United States ; (6) Fremantle, Australia ; (7) Calgary, Canada ; (8) Rochester, United States ; (9) Kiel, Germany ; (10) Los Angeles, United Stated ; (11) Amsterdam, Netherlands ; (12) Leuven, Belgium.

Objectives : Natalizumab, a humanized monoclonal IgG_4 antibody to α4 integrin, was evaluated in a randomized, controlled study (ENACT-2) to determine the ability of a 12-month regimen to maintain clinical response/remission that had been achieved by patients receiving natalizumab in a phase 3 induction of response/remission study (ENACT-1).

Methods : Adult patients (n = 339) with Crohn's disease (CD) who achieved response (e70-point reduction in baseline CD Activity Index [CDAI]) and/or remission (< 150) and had a CDAI score < 220 after receiving natalizumab in the induction study (ENACT-1) were re-randomized 1 :1 to natalizumab 300mg (n = 168) or placebo (PLC) (n = 171) and received up to 12 additional monthly infusions in ENACT-2. The primary and contingent primary endpoints were the proportion of patients that maintained response and the proportion of patients that maintained remission at every time-point through an additional 6 months of therapy, respectively.

Results : Through 6 months, 61 % (103/168) of natalizumab-treated patients maintained clinical response vs 28% (48/171) of patients re-randomized to PLC ($p < 0.001$), and sustained clinical remission was maintained by 44 % (57/130) vs 26 % (31/120), respectively ($p = 0.003$). Through 12 months, 54 % (90/168) of natalizumab-treated patients maintained clinical response vs 20 % (34/170) re-randomized to receive PLC ($p < 0.001$). Sustained clinical remission was maintained by 39 % (51/130) of natalizumab-treated patients through 12 months vs 15 % (18/120) in the PLC group ($p < 0.001$). Additionally, through 6 months, 58% (39/67) of natalizumab-treated patients taking steroids in ENACT-1 and re-randomized to natalizumab in ENACT-2 were withdrawn from steroids, compared with 28% (21/76) on PLC ($p < 0.001$). Through 12 months, 49 % (33/67) of natalizumab-treated patients taking steroids in ENACT-1 and re-randomized to natalizumab in ENACT-2 were withdrawn from steroids, compared with 20 % (15/76) for PLC ($p < 0.001$). No clinically significant differences in the rates of serious and non-serious adverse events between treatment groups were observed.

Conclusions : Natalizumab is significantly more effective than PLC for the maintenance of response and remission through 12 months of treatment in patients with CD who respond to induction therapy with natalizumab. Monthly administration of natalizumab for 12 months was well tolerated and allowed complete withdrawal of steroids in a significant number of patients.

- D15 -

SENTINEL LYMPH NODE MAPPING IN COLON CANCER : A FEASABILITY STUDY. S. Laurent, B. Detroz, O. Detry, A. Thiry, J. Boniver, J. Belaiche, M. Meurisse. CHU LIEGE.

Backgrounds : 15 % to 25 % of patients suffering of Dukes B colorectal cancer will develop recurrence within the 5 years of the diagnosis in spite of a presumably curative surgery. Under staging of the nodal status could be the explanation of those recurrences. The sentinel lymph node (SLN) technique seems to be a solution with the specific analyse of 'the theorically more suspect node'. The aim of this study was to evaluate the feasibility and interest of sentinel node detection to identify the ultrastaging rate detecting occult micrometastases missed on routine Hematoxyllin Eosin (H&E) examination.
Methods : During surgery blue dye was injected subserously around the tumour in 32 patients operated for a colon cancer. The first lymph nodes to turn blue were noted as SLN. The standard histopathologic examination was performed for each case. For each sentinel lymph node three examination levels were performed ; if no tumour was detected by Hematoxylin Eosin examination, a cytokeratine immunohistochemistery (HIC) study was performed.
Results : At least one SLN could be intraoperatively identified in 31 patients (99.2 %).The median number of lymph nodes examined and of sentinel lymph nodes was, respectively, 13.76(range 1-30) and 1.6 (range 1-4). Among the 24 pN0 patients whom the SLN was found, 10 benefited of an ultrastaging. Among the seven pN+ patients, two patients presented negative SLN in H&S and IHC (2/32 6.25 % false negative).
Conclusions : Sentinel lymph node detection was a successful technique with 99.2 % of feasibility when there was no evident lymph node involvement, no associated metastasis and no previous colic surgery. Focused examination of the sentinel lymph node identified 41.66 % of additional ultrastaging disease for TxN0M0 tumour. This could change therapeutic attitude for adjuvant chemotherapy.

- D16 -

DETAILED AND UNIFORM PATHOLOGICAL EVALUATION OF CIRRHOTIC EXPLANT LIVERS REVEALS HEPATOCELLULAR CARCINOMAS WITH NUMEROUS SMALL INTRAHEPATIC METASTASES AND GIVES NEW INSIGHTS INTO TUMOR PROGRESSION. L. Libbrecht (1), D. Cassiman (2), C. Verslype (2), T. Roskams (1). (1) Department of Pathology, University Hospitals Leuven ; (2) Department of Hepatology, University Hospitals Leuven.

Most studies on hepatocellular carcinoma (HCC) in explant livers apply a broad liver sectioning with variable slice thickness. Consequently, some HCCs remain undetected and pathological staging is inaccurate, biasing conclusions of these studies. We recently proposed 'golden standard' pathological evaluation of explants. This **method** includes uniform liver slicing at 5-mm intervals with biopsies of each macroscopical lesion followed by microscopical classification.This 'golden standard' method was applied on 108 cirrhotic explant livers. When possible, HCCs were classified as primary or intrahepatic metastasis (IM) according to WHO-guidelines. Predominant differentiation and microvascular invasion was noted.One or more HCCs were present in 32 patients (30 %). Three livers in which presumed HCC(s) were completely destroyed by pretransplant treatment and 2 livers in which not all HCCs could be confidently classified as primary or IM were excluded. 11 of the remaining 27 patients (40 %) had at least one IM ; the mean diameter of IMs was 4.3 mm (range 2-10). Six patients (22 %) had a HCC with at least 3 IMs (maximum : 27 IMs) and thus exceeded UNOS-criteria. Due to their small size, IMs were rarely detected during pretransplant imaging ; only the primary, larger HCC was detected. Two patients with multiple IMs in their explant liver died of HCC recurrence during mean follow-up of 17 months. IMs were only seen in HCCs larger than 20 mm. An increase in diameter of primary HCC was associated with an increase in IM number, a poorer differentiation and frequent microvascular invasion ($p < 0.0005$). Six primary HCCs were outliers from this pathway : 3 were large (> 5cm), but were still well differentiated and showed neither microvascular invasion nor IMs. Conversely, 3 HCCs showed prominent microvascular invasion and had much more IMs (between 9 and 27) than expected according to their diameter (between 35 and 60 mm).
Conclusion : patients with numerous small IMs in their explant liver can only be recognized by the 'golden standard' pathological evaluation. There is a general HCC progression pathway in which increase in diameter is closely linked with decreased differentiation and increased IM number. Some HCCs deviate from this pathway and are either metastasis-resistant or metastasis-prone.

- D17 -

ROLE OF NASAL POTENTIAL DIFFERENCE MEASUREMENT IN THE DIAGNOSIS OF IDIOPATHIC CHRONIC PANCREATITIS. P. H. Deprez (1), P. Lebecque (2), P. Wallemacq (3), J. F. Gigot (4), Y. Horsmans (1), T. Leal (3). (1)Gastroenterology Dpt ; (2) Pediatry Dpt ; (3) Clinical Chemistry Dpt ; (4) Digestive Surgery Dpt ; Cliniques universitaires St-Luc, Universite Catholique de Louvain, Av Hippocrate 10, Brussels.

Background : Idiopathic chronic or recurrent pancreatitis remains a clinical diagnostic challenge even in the era of molecular biology. Single allelic or compound heterozygous CFTR mutations have been associated with chronic idiopathic pancreatitis. Nasal potential difference (NDP) measurement has been proposed to assess defective ion transport in cystic fibrosis (CF).
Aim : evaluate NDP in patients with idiopathic pancreatitis and CFTR mutations and clarify the contradictory results obtained with NDP measures in the literature.
Patients and methods : pts with chronic pancreatitis, diagnosed by helical CT, MRI, EUS or ERCP, with no history of hereditary pancreatitis, alcohol intoxication or metabolic disease and presenting with a CFTR mutation, but no lung disease, were included. Five pts underwent endoscopic or surgical ductal drainage. Interestingly, 2 pts presented adenocarcinoma and 1 IPMT during follow-up of mean 6.8 y [range 2-14]. Two pts developed diabetes and 3 pts exocrine pancreatic insufficiency. NDP was measured with a simplified method based on nasal instillation in supine position at reduced flow rates (Leal 2003). These results were compared with those of CF pts (n = 21) and controls (n = 34).
Results : 10 patients (9 men,1 woman), mean age 32 years (24-59) presented for 3 of them a G542X mutation, 1 a R117H, 1 a DF508 and 4 an intron 8 “5T allele”. Mean sweat chloride values were normal : 28.7 mmol/L [range 11-49]. NPD measures showed normal baseline values (13.4 mV [7-20] vs 16.6 [7-31] in controls and 44.9 [16-62] in CF, and normal inhibition after instillation of amiloride in baseline solution. Significant decreases of voltage cumulative changes were however observed after instillation of low Cl^- solution plus amiloride : 4.9 [1-9] in patients vs 10.4 [3-17] in controls ($P < 0.001$) and 1.9 [-17-+19] in CF, and after low Cl^- solution instillation containing isoprenaline and amiloride 8.8 [0.5-18] vs 15.5 [7-31] ($P < 0.005$) in controls and 4.2 [-16-+26] in CF patients.
Conclusions : significantly abnormal NPD values were observed after pharmacological stimulation in all patients evaluated for idiopathic chronic pancreatitis and heterozygous mutations of the CFTR gene. This reflects abnormal Cl-secretion and could explain the pancreatic symptoms. This easy and inexpensive test should be proposed to these patients, before genetic testing, since mutational screening of the entire CFTR gene cannot be considered in every patient with idiopathic pancreatitis.

- D18 -

DEFECTIVE HEPATIC REGENERATION AFTER PARTIAL HEPATECTOMY TO LEPTIN DEFICIENT OB/OB MICE IS NOT RESCUED BY EXOGENOUS LEPTIN ADMINISTRATION. I. Leclercq (1), M. Vansteenberghe (2), V. Lebrun (1), P. Starkel (1), C. Picard (1), Y. Hosrmans (1). (1) Laboratoire de Gastro-entérologie ; (2) Laboratoire de Chirurgie Experimentale, ULC, Brussels.

Ob/ob mice have impaired liver regeneration attributed to leptin deficiency.
Aim : We tested the effects of leptin replacement on regenerative response to partial hepatectomy (PH) in ob/ob mice.
Methods : Activation of the priming phase and hepatocyte proliferation were analysed after a 55 % PH.
Results : 55 % PH to ob/ob mice was associated with defective regeneration : there were rare and significantly less mitotic figures, BrdU positive, Ki67 positive hepatocyte nuclei or PCNA up-regulation than in lean mice 44 hours after PH. Leptin replacement (100 µg/Kg body weight twice daily) restored normal circulating leptin levels and restrained the hyperactivation of transcription factors STAT-3 and AP-1 observed in ob/ob mice during the priming phase, but did not improve liver regeneration. Correction of the metabolic abnormalities of ob/ob mice (obesity, insulin resistance, hepatic steatosis) by food restriction (with or without leptin-repletion) or by leptin injections during 3 weeks prior to PH, similarly failed to induce any significant hepatocyte proliferation or expression of PCNA. Leptin is an important factor for macrophage and Kupffer cells function and cytokine production. The normal rise in hepatic TNF protein and IL-6 mRNA induced by PH was almost completely prevented in ob/ob mice. Moreover, exogenous leptin failed to correct TNF and IL-6 expression and to rescue liver regeneration after PH to *ob/ob* mice.
Conclusion : Liver regeneration is deeply impaired in *ob/ob* mice. We have conclusively shown that nor leptin replacement, nor attenuation of activation of transcription factors in the priming phase, nor amelioration of the metabolic syndrome and hepatic steatosis, with or without restitution of normal circulating levels of leptin, was able to restore replicative competence to *ob/ob* mice. All this strongly suggests that leptin does not directly signal on hepatocytes to allow the regenerative process. In addition, leptin replacement was not sufficient to favour the release of key cytokine mediators of proliferation such as TNF and IL-6. These results support the concept that leptin-deficiency renders the Kupffer cells (and maybe other liver cells) unable to release key mediators and cytokine to drive cell proliferation in the setting of partial hepatectomy.

- D19 -

RANDOMISED DOUBLE-BLIND CROSS-OVER STUDY EVALUATING THE EFFECT OF INTRAPYLORIC INJECTION OF BOTULINUM TOXIN ON GASTRIC EMPTYING AND SYMPTOMS IN PATIENTS WITH GASTROPARESIS. J. Arts, P. Caenepeel, T. Degreef, K. Gebruers, K. Verbeke, J. Janssens, J. Tack. Dept. of Gastroenterology, UZ Gasthuisberg, KU Leuven.

Recent uncontrolled studies suggested potential benefit of intrapyloric injection of botulinum toxin (botox) in idiopathic and diabetic gastroparesis (Lacy 2002, Miller 2002, Arts DDW 2003). On the other hand, controlled studies with gastroprokinetic drugs found significant placebo effects on gastric emptying rates and on symptoms (Talley 2001 ; Tougas DDW 2003 ; Fang DDW 2004 ; Holtmann DDW 2004).
Aim : To perform a double-blind placebo-controlled cross-over study to investigate the effects of botox injection on gastric emptying rate and symptoms in gastroparesis.
Methods : 12 patients with known gastroparesis (8 women, mean age 44 ± 11 years, 2 diabetic and 9 idiopathic) participated in the trial. They underwent two upper g.i. endoscopies with 4 weeks interval during which they received intrapyloric injection with saline or botox 4x25U in a randomised double-blind fashion. Injections were prepared by a nurse who was otherwise not involved in the care of these patients. Before the start of the study and 4 weeks after each treatment, they filled out a symptom questionnaire rating 9 gastroparesis symptoms on a scale from 0-5, and underwent a solid and liquid gastric emptying breath test using ^{14}C octanoic acid and ^{13}C glycin. Total symptom scores and gastric half emptying times (t1/2) were calculated and compared using Student's t test.
Results : Pooled data showed significant improvement of solid emptying t/2 after botox injection (112 ± 25 vs. 96 ± 26 min ; $p < 0.05$) but not after saline (99 ± 32 vs. 87 ± 27 min ; $p = 0,3$). In contrast there was no significant changes of the gastroparesis score in the sham or in the active groups after one month, but symptoms improved after cross-over in both groups (respectively $p < 0.05$ and $p = 0.06$).
Conclusion : In the interim analysis after the first 12 patients in this ongoing placebo-controlled, cross-over study, intrapyloric injection of botox in gastroparesis patients enhanced solid gastric emptying, but had no significant influence on symptoms.

- D20 -

HIGH RADIOLOGICAL INCIDENCE OF TRACT METASTASES AFTER PERCUTANEOUS ABDOMINAL CT-GUIDED CORE BIOPSY. J. de Mey, B. Op de Beeck, F. Vandenbroucke, L. Trappeniers, A. Bossuyt, G. Storme, J. De Greve. AZ VUB Brussels.

Purpose : To evaluate the CT-scan incidence of tract metastases after percutaneous abdominal core biopsies and to evaluate the influence of puncture technique and tumour characteristics.
Patients and methods : Data on 214 cases of percutaneous CT-guided core biopsies (16 or 18 gauge) over a six-year period were analysed. Needle tract and surrounding tissue were compared and evaluated on the puncture and the control scans.
Results : Radiological incidence was 14 on 214 (6.5 %). In the subgroup of the non-coaxial guided biopsies, incidence was even higher : 13 on 102 (13 %). Tract metastasis was detected after a mean period of 372 days and in this way, due to short follow up, the incidence is probably even underestimated. Two tract metastases did occur subcutaneously, all the others were located under the abdominal wall. Biopsy of a pancreatic lesion (2 tract metastases on 10 interventions = 20 %) and biopsy of a cholangiocarcinoma (2 tract seeding on 6 = 33.3 %) or melanoma (2 tract seeding on 8 = 20 %) were very high-risk procedures. None of the patients died due to the tract metastases. All tract-seeding lesions, except one, were detected when the patients were already in a palliative setting. Patient survival after detection of the tract metastases was short (mean 3 months).
Conclusion : The risk for metastases after a non-coaxial percutaneous abdominal large core biopsy is very high, however the clinical impact of these tract metastases is low. A coaxial biopsy technique reduces the risk with more than a factor 10.

- D21 -

LONG-TERM FOLLOW UP OF ENDOLUMINAL ANTI-REFLUX PROCEDURES FOR GERD : SINGLE-CENTER EXPERIENCE WITH 3 PROCEDURES. J. Arts (1), P. Caenepeel (1), D. Sifrim (1), T. Lerut (2), P. Rutgeerts (1), J. Janssens (1), J. Tack (1). (1) Dept. of Gastroenterology, UZ Gasthuisberg, KU Leuven ; (2) Dept. of Thoracic Surgery, UZ Gasthuisberg, KU Leuven.

During the last few years, a number of endoscopic anti-reflux procedures (EARP), aiming at per-endoscopic improvement of the barrier function at the lower esophageal sphincter (LES), have emerged. Techniques include creation of plications (Endocinch® or ESD®), injection of inert material (Enteryx®) or delivery of radiofrequency-energy (Stretta®), and several studies reported short-term efficacy.
The **aim** of this study was to evaluate the long-term efficacy of EARP on symptoms, anti-secretory drug use and pH monitoring in a single center.
Methods : All GERD patients who underwent EARP at our centre before 2004 were prospectively followed using endoscopy, pH monitoring, and questionnaires for heartburn and PPI use. All data are given as mean ± SD and were analyzed by paired Student's t test.
Results : Seventy-one patients underwent a Endocinch® or ESD® (n = 36), Enteryx® injection (n = 7) or a Stretta® procedure (n = 28). After a mean follow up of 2.5 ± 0.8 years, reflux scores had significantly improved in the Endocinch®/ESD® and Stretta® groups (table), but none of the procedures led to an important decrease of acid exposure. PPI use was stopped in only 14 to 32 % and reduced in 14 to 22 %. Long-term complications were loss of sutures in the Endocinch® group (2.0 ± 0.4 to 1.5 ± 0.8 after one year, $p < 0.05$) and oesophageal stenosis requiring repeated dilations (n = 10) in one Enteryx® patient.Fourteen patients (20 %) were referred for anti-reflux surgery.
Conclusion : In spite of significant symptom improvement, long-term evaluation after EARP in this single-center experience showed ongoing PPI use in the majority of patients and lack of normalisation on pH monitoring. Additional studies are needed to determine which patients, if any, may respond to these procedures.

	Endocinch/ESD (n = 36)	Stretta (n = 28)	Enteryx (n = 7)
Symptom score	12 ± 1 to 6 ± 4*	11 ± 2 to 6 ± 1*	16 ± 4 to 14 ± 4
Surgery	9 (25%)	2 (7%)	3 (43%)
PPI stop/decrease (%)	25 % / 22 %	32 % / 21 %	14 % / 14 %
% time pH < 4	15 ± 2 to 9 ± 1*	16 ± 2 to 11 ± 2	13 ± 4 to 15 ± 5

* $p < 0.05$

- D22 -

LONG-TERM OUTCOME OF ACHALASIA THERAPY WITH PNEUMATIC DILATION FIRST IN A TERTIARY CARE CENTER. M. Hulselmans (1), D. Sifrim (1), W. Coosemans (2), T. Lerut (3), J. Janssens (1), J. Tack (1). (1) Department of Gastro-Enterology ; (2) Department of Transplant Surgery ; (3) Department of Thoracic Surgery, UZ Gasthuisberg, Leuven, Belgium.

Management of achalasia is based on pneumatic dilation or Heller myotomy, but recent studies suggest poor long-term outcome. The **aim** of the present study was to perform an audit of the long-term outcomes of achalasia treatment with initial pneumatic dilations, and to study the factors associated with successful outcome.
Methods : All achalasia patients treated with pneumatic dilation between 1992 and 2002 were contacted for a follow-up questionnaire. Correlations with demographics, presenting symptoms, manometric features and treatment variables were analysed using chi-square and Student t-testing.
Results *:* Of a total of 225 patients (118 men, mean age 52.2 ± 1.4 years), diagnosed with achalasia between 1992 and 2002, 71 % responded to the questionnaire. All patients were initially treated with consecutive esophageal dilations up to balloon diameters of 3.0 (26 %), 3.5 (41 %), or 4.0cm (33 %). At 1-month follow-up, mean LES pressure had decreased from 31.8 ± 1.2 mm Hg to 17.3 ± 0.8 mm Hg ($p < 0.0001$), dysphagia had decreased from 96 to 27 % and 49 % had gained on average 4.6 ± 0.5 kg (weight loss at presentation in 39 % of on average 10.8 ± 0.7kg). During follow-up, 67 % required no additional treatment, and 23 % required repeat dilations after a median of 5 years. Thirty seven non-responders received botox injection (n = 19) or underwent surgery (n = 26). After a median follow-up of 70 months, 67 % were free of dysphagia, 89 % had regained body weight, 11 % reported heartburn and 16 % reported PPI intake. Excellent, or good treatment outcomes were obtained in 71 % of the patients, with no significant difference between patients requiring single or repeat dilations (respectively 74 and 66 %). Favorable outcome was not influenced by initial or post-treatment LESP, the presence of vigorous achalasia, or PPI need. Successful outcome of rescue therapy was obtained after surgery (85 %), but not with botox (44 %). Patient satisfaction was high with respectively 21, 27 and 33 % of the patients reporting excellent, very good or good treatment outcome satisfaction.
Conclusions : Management with initial dilations and surgery for short-term failures yields to good or excellent long-term results in over 70 % and treatment satisfaction in over 80 % of patients. Management of dilation failures is more problematic.

- D23 -

CAN PIECEMEAL MUCOSECTOMY BY EMR-C REMOVE BARRETT'S ESOPHAGUS WITH HIGH GRADE DYSPLASIA OR ADENOCARCINOMA ? P. H. Deprez (1), T. Aouattah (1), C. Sempoux (2), J. Grodos (2), R. Fiasse (1), Y. Horsmans (1), H. Piessevaux (1). (1) Dpt of Gastroenterology, (2) Dpt of Pathology, Clin. Universitaires Saint-Luc, Université catholique de Louvain, Av. Hippocrate 10, 1200 Brussels.

Aim : Prospective evaluation of piecemeal mucosectomy using the cap method (EMR-c) in patients presenting with Barrett's esophagus and high grade dysplasia of superficial adenocarcinoma and aiming at complete removal of the neoplastic lesion and the intestinal metaplasia.
Patients and methods : Inclusion criteria : long or short Barrett's esophagus with high grade dysplasia or T1m N0 adenocarcinoma staged by radial or linear Pentax EUS scope (EG-3630-UR or EG-3830-UT) with the Hitachi EUB 6500 processor and 20MHz miniprobe. Resection was performed under general anesthesia, starting at the site of the tumour, after submucosal injection of 2-5 ml aliquots of saline for a total of 10-50 ml, than resecting the remaining Barrett's mucosa from anal to oral direction. Circonferential resection was avoided if the height of Barrett's metaplasia exceeded 1 cm. Oblique or straight transparent rigid cap was used and resection was completed if necessary by APC (0.6 L, 60 W) for residual bridging or short remaining tongs of metaplasia. Patients were discharged one or two days after mucosectomy under liquid diet and omeprazole 40mg bid was started before treatment and continued for 8 weeks minimum.
Results : 20 patients (mean age 68y, range 47-85, 3 women/17 men) were included with HGD in 15 and mucosal adenocarcinoma in 5. Circonferential length of Barrett's mucosa (C) was 19 mm (5-70) and highest limit (M) 26 mm (5-80). A total of 26 EMR-c sessions were performed (1.3 ; 1-5), removing 95 specimens (4.8 ; 1-13 per patient). Follow-up is now 13.3 months (3-38 months). Successful resection of HGD and adenocarcinoma was observed in all patients. Complete removal of intestinal metaplasia was observed in 65 % of patients (13/20), with 2 patients still presenting low grade dysplasia. Remaining Barrett's mucosa was however limited to sections of < 5 mm in 6/7 patients. Complications occurred in 4 patients : 3 minor bleeding episodes during EMR treated by endoscopic hemostasis (APC or hemoclip) and 1 oesophageal stricture requiring endoscopic dilatation.
Conclusions : Although EMR-C piecemeal resection is acceptable for treatment of intraepithelial or mucosal adenocarcinoma complicating Barrett's esophagus, it is only successful in 2/3 of patients when aiming at complete resection of intestinal metaplasia. Improvements in endoscopic techniques of esophageal mucosectomy and new appropriate devices to improve efficacy and safety are mandatory to obtain higher success rates.

- D24 -

PATIENTS WITH CHRONIC COUGH NOT RESPONDING TO STANDARD PPI THERAPY MAY HAVE PERSISTING COUGH ASSOCIATED WITH WEAKLY ACIDIC REFLUX. K. Blondeau (1), L. Dupont (2), X. Zhang (1), J. Tack (1), J. Janssens (1), D. Sifrim (1). (1)Center for Gastroenterological research KULeuven ; (2) Pneumology Department KULeuven.

A subgroup of patients with suspected acid reflux-induced cough do not respond to standard dose PPI treatment. Recently, we have demonstrated that weakly acidic reflux might be associated with chronic cough. We investigated whether weakly acidic reflux is involved in chronic cough refractory to PPI therapy.
Methods : Chronic cough patients refractory to standard dose PPI (n = 21), were studied with ambulatory manometric-impedance-phmetry. Out of these, 16 [9 men, 53 years (30-81)] were studied 'off' PPI, and 5 [2 men, 63 years (51-73)] were studied 'on' PPI therapy. Esophago-gastric manometry was used for precise recognition of cough. Reflux was assessed with impedance-pH monitoring and defined as acid (pH < 4), weakly acidic (pH 4-7) and weakly alkaline (impedance drops with pH 7). Cough was considered 'induced by' reflux, if it started in a 2 min period after a reflux event. A Symptom Association Probability (SAP) was calculated for each type of reflux in every patient and considered positive if > 95 %.
Results : In patients studied 'off' PPI, a total number of 588 cough bursts [31, (5-111)]/pat and 842 reflux events [58, (5-76)]/pat were analyzed. Reflux events were classified as acid (n = 542) [34(2-63)]/pat, weakly acidic (n = 213) [15(1-34)]/pat and weakly alkaline (n = 53) [1(0-15)]/pat. From the total number of cough, 100 (17 %) were considered 'induced by' reflux (61 acid, 33 weakly acidic and 6 weakly alkaline). The per-individual analysis showed a SAP+ for acid reflux in 2 patients, weakly acidic reflux in 4 patients and for both acid and weakly acidic reflux in 2 patients. In patients studied 'on' PPI, a total number of 220 cough bursts [24(3-145)]/pat and 237 reflux episodes [40(35-75)]/pat were recorded. Thirty-three reflux episodes involved acid reflux [3(1-23)]/pat, 163 weakly acidic [31(0-29)]/pat and 41 weakly alkaline [8(1-22)]/pat. In this group, 50 cough events (22.8%) were considered to be 'induced by' a reflux episode (6 acid, 42 weakly acidic and 2 weakly alkaline). The per-individual analysis showed 2 patients with SAP+ for weakly acidic reflux. In total 8/21 patients had a SAP+ for weakly acidic reflux.
Conclusion : In a group of patients with reflux-associated chronic cough, PPI treatment changes the acidity of the refluxate without eliminating the cough. In these patients, weakly acidic reflux might be the cause of persisting cough and an anti-reflux strategy either pharmacological or surgical could be considered.

- D25 -

DETERMINANTS OF DECREASED QUALITY OF LIFE IN FUNCTIONAL DYSPEPSIA. S. Kindt (1), D. Dubois (2), P. Caenepeel (1), J. Arts (1), L. Van Oudenhove (1), J. Tack (1). (1) Department of Gastro-Enterology, UZ Gasthuisberg, Leuven, Belgium ; (2) Johnson & Johnson Pharmaceutical Services, Beerse, Belgium.

Background : The PAGI-QOL© and PAGI-SYM© questionnaires were recently validated for evaluation of quality of life and therapeutic responsiveness in functional dyspepsia (FD). FD is a heterogeneous disorder, with different pathophysiological mechanisms underlying its symptoms. It is unknown which mechanisms contribute most to FD symptoms accounting for a perceived loss in quality of life (QOL).
The **aim** of this study was to investigate the relationship between gastric sensorimotor dysfunction, FD symptoms and a decline in perceived quality of life in FD.
Methods : 164 consecutive patients underwent Helicobacter pylori screening, barostat testing and standardized gastric emptying testing (n = 126), and they completed the PAGI-QOL and PAGI-SYM questionnaires. 1/ Correlations between the scores for the five PAGI-QOL subscales (daily activities, clothing, diet/food, relationship, psychological well-being) and the six PAGI-SYM subscales (nausea/vomiting, postprandial fullness/early satiety, bloating, upper abdominal pain, lower abdominal pain, heartburn/regurgitation) were assessed. 2/ Correlations between the PAGI-QOL and results of gastric function testing (pressures and volumes inducing first perception and discomfort, gastric accommodation, solid emptying t1/2) were investigated. Statistical analysis consisted of Pearson's linear correlation, multiple regression, Student t and Chi-Square testing.
Results : 1/ PAGI-QOL and the PAGI-SYM subscales were highly correlated to each other ($r < -0.15$, all $p < 0.05$). Multiple regression indicated significant correlations between fullness/satiety and the QOL domains of daily activities, diet/food and psychological well-being (all $p <= 0.01$) and between nausea/vomiting and the QOL domains of daily activities ($p = 0.02$) and relationship ($p = 0.03$). The highly significant correlation between clothing and bloating ($r = -0.67$) was confirmed ($p < 0.0001$). Upper abdominal pain and heartburn/regurgitation were highly correlated to diet/food habits ($p = 0.02$ and 0.04 respectively). At different cut-off levels, poorer scores for PAGI-QOL subscales were consistently associated with more severe scores for PAGI-SYM subscales. 2/ There was a significant correlation between pressure inducing discomfort and daily activities score ($r = 0.16$, $p < 0.05$). Significant correlations were found between the volume at discomfort and scores for daily activities, clothing and diet/food (all $r = 0.17$, $p < 0.05$). Patients with hypersensitivity to gastric distention had poorer scores for daily activities and diet/food (both $p <= 0.05$). At different cut-off levels, consistent associations were found between discomfort volume and diet/food only.
Conclusion : Pathophysiological disturbances (especially visceral hypersensitivity) as well as the intensity of several FD symptoms account for the perceived loss in quality of life, mainly trough their impact on daily activities and diet/food.

- D26 -

LONG-TERM OUTCOME IN TERTIARY CARE FUNCTIONAL DYSPEPSIA PATIENTS. L. Mispelon, S. Kindt, P. Caenepeel, J. Arts, J. Janssens, J. Tack. Department of Gastro-Enterology, UZ Gasthuisberg, Leuven, Belgium.

Background : A number of studies have reported on the evolution over time of dyspeptic symptoms in the general population (Talley 1992, Lindell 1995, Agreus 1995), but very little is known about the longer-term outcome in patients with functional dyspepsia (FD). FD is a heterogeneous disorder, with different pathophysiological mechanisms underlying the symptom pattern. The **aim** of this study was to prospectively evaluate the evolution of symptoms in FD patients, seen at a tertiary care center, and to identify factors that influence outcome.
Methods : Using telephone interviews and mailed questionnaires, we prospectively followed up FD patients, who underwent a complete pathophysiological investigation. Patients were contacted twice over the last 4 years and were asked to indicate whether their symptoms had worsened, stayed the same, improved or disappeared. Symptom outcome was correlated to demographics, symptom pattern, Helicobacter Pylori status, gastric emptying rate, gastric sensitivity and gastric accommodation at presentation using chi-square and Student t-tests.
Results : A response was obtained in 197 of 285 contacted patients (69 %). After a mean follow-up of 26 ± 5 months, only 2 % of patients reported disappearance of symptoms and 20 % reported improvement. After a mean follow-up of 63 ± 5 months, disappearance of symptoms was reported by 22 %, improvement by 44 %, no change by 29 % and worsening by 5 %. Younger age at presentation (35 ± 1 vs. 42 ± 1, $p < 0.005$), less weight loss (4 ± 1 vs. 7 ± 1 kg, $p < 0.05$) and less delayed gastric emptying (t1/2 87 ± 5 vs. 107 ± 20 min, $p < 0.05$) were significant predictors of symptom disappearance at 5 years follow-up. Patients with worsening at late follow-up were less likely to report acute onset (20 % vs. 47 %). Sex, gastric sensitivity, HP status and gastric accommodation were no predictors of long-term outcome.
Conclusion : Although 2-years outcome is poor, the majority of tertiary care FD patients reports improvement or disappearance of symptoms after 5-years follow-up. Younger age, normal gastric emptying rate and limited weight loss at presentation are predictors of long-term favourable outcome.

- D27 -

COLORECTAL CANCER DIAGNOSIS IN A BELGIAN PROVINCE : CHALLENGES AND PITFALLS IN SCREENING AND EARLY DIAGNOSIS. M. Polus (1), G. Houbiers (2), H. Kalantari (3), I. Paul (4), G. Daenen (5), A. Frère (6), C. Gillard (6), C. Van Kemseke (1), E. Mohr (1), B. Delhougne (6), J. Belaiche (1), J. Reginster (4), E. Louis (1), S. Liégeoise de Gastroentérologie. (1) Gastro Unit, CHU Liège ; (2) Gastro Unit, CHBAH Seraing ; (3) Oncology Unit, Hopital de Verviers ; (4) Département de Santé publique, ULg ; (5) Gastro Unit, CHU-NDB Liège ; (6) Gastro Unit, CHR citadelle, Liège.

Colorectal cancer (CRC) is a preventable disease through early detection and treatment. Yet, screening rate remains low and diagnostic procedure delayed in some patients. Hence, mortality rate remains high in the Belgian population. While population based CRC screening depends on a political decision, targeted screening in high risk population and early diagnosis is linked to good clinical practice. Our aim was to characterize the CRC diagnostic procedure in the province of Liège to try and identify challenges and pitfalls in screening and early diagnosis.
Methods : We performed a multicenter prospective case-based study of patients with CRC. A representative group of gastroenterologists and abdominal surgeons of a Belgian province took part in the study and recorded all the new CRC cases they diagnosed between October 2002 and October 2004. Two hundred and seven patients were included. Detailed information concerning socio-economical status of patients, presentation of the disease, delay between symptom's presentation and medical exploration for diagnosis was obtained from patient's history. Information concerning cancer was abstracted from the pathology reports and medical records.
Results : Only < 5 % of the population (10/207) had undergone at least one screening exploration previously to colorectal cancer diagnosis. Although significantly higher than in the general population, the screening for the high risk subgroup with CRC family history was still low (4/23 : $P < 0.05$). Overall, early tumors T1-T2 represented 12 % of cases, T3 : 48% and T4 : 25 %. Nodal involvement concerned 45 % of tumors and distant metastases was found in 22 % of all the cases. The stage at diagnosis was not statistically different for the high risk patients. More than one third of high risk patients (38%) had a late-stage disease with distant metastases at the initial presentation. The delay between initial symptoms and the time of diagnosis was more than 6 months for a significant part of the population (20 %). Again this delay was not significantly shorter in the high risk population. High educational status was predictive of earlier disease stage at diagnosis ($p < 0,05$).
Conclusions : These results suggest that screening is not yet enough proposed in our population, particularly for the high risk patients with well documented family history of CRC. The delay between symptoms and diagnosis could also be shorten in some cases. Such local data may help to inform population and general practitioners about the importance of early diagnostic procedure and interest of targeted screening in high risk patients.

- D28 -

DIAGNOSTIC YIELD OF SCREENING COLONOSCOPY FOR COLORECTAL NEOPLASM : A EUROPEAN STUDY. M. Suball, A. Demols, J. Devière, P. Eisendrath, O. Le Moine, N. Nagy, A. Van Gossum, J. Van Laethem, M. Adler. Hôpital Erasme, Brussels.

With the increasing use of colonoscopy as a primary screening modality for colorectal cancer (CRC) screening in average risk (i.e. above 50 y.o. people), knowing the detection rate and colonic distribution of colorectal neoplasms (i.e. adenomas and cancer) is of utmost importance. Such informations including endoscopic and pathological data are available only from two US ([1,2]) and one Chinese ([3]) series. This study is a retrospective analysis of 555 consecutive persons aged 50 and over submitted in our unit to a screening colonoscopy between June 1999 and March 2002. Exclusion factors included a recent (6 months) history of digestive alarm symptoms, a previous diagnostic test, previous surgery of the colon or personal history of CRC neoplasms. A family history (one or more first-degree relatives) of CRC was present in 61 persons (11 %). Mean (± SEM) age was 62.4 (± 9.8) and 62 % were male. A polypoid lesions was discovered endoscopically in 230 persons (41.4 %) : 1, 2, 3 and more than 3 polyps in 48.6 %, 28%, 12 % and 12 %. These lesions were distal (within the last 40 cm of the colon) in 52 %, proximal and distal in 23 % and proximal alone in 25 %. Adequate pathological specimens lesions and classified according to the WHO recommendation were available in 206 of 220 lesions : 47 (23 %) were hyperplastic polyps, 136 (66 %) were neoplasms (i.e. adenomas or cancer) and 23 (11 %) were miscellaneous findings. The overall respective diagnostic yield for colorectal neoplasms, advanced neoplasia (i.e. adenoma 10 mm, villous adenoma, high grade dysplasia or intramucosal carcinoma), invasive cancer and proximal advanced neoplasia or invasive cancer without any distal findings were : 24.5 %, 8.2 %, 0.7 % and 2 %. In conclusion, our figures compare favourably with the diagnostic yield reported in the US and Chinese series despite differences in ethnicity and they could be considered as the standard to be achieved by all endoscopists screening populations aged older than 50 years for CRC.

1. Imperiale, NEJM 2000 ; 2. Lieberman, NEJM 2000 ; 3. Sung, Gastroenterology 2003

- D29 -

MULTICENTRIC BELGIAN EXPERIENCE IN THE DETECTION OF SMALL BOWEL MALIGNANCY BY USING VIDEO CAPSULE ENDOSCOPY. D. Urbain (1), D. De Looze (2), I. Demets (3), E. Louis (4), O. Dewit (5), E. Macken (6), A. Van Gossum (7). (1) AZ VUB ; (2) UZ Gent ; (3) Gasthuisberg, KUL ; (4) CHU de Liège ; (5) St-Luc, UCL ; (6) UZ Antwerpen ; (7) Erasme, ULB.

Background : Early detection of small bowel (SB) tumors is crucial for initiating appropriate therapy. However, this diagnosis remains difficult due to the endoscopic inaccessability of this organ. There are no data available in Belgium concerning the place of the Video Capsule Endoscopy (VCE)for the diagnosis of SB tumors.
Aim :To evaluate the impact of VCE on the diagnosis as well as on the therapy of SB malignancy by collecting data from the 7 academic hospitals.
Methods : The following information was asked : indication for VCE, diagnostic procedures before VCE,description and localisation of the lesion, influence of the VCE findings on therapy, final diagnosis.
Results : A total of 433 VCE were performed in the different centers until November 2004. Eleven malignant processes of the SB were identified by VCE (2,3 %). Sex ratio M/F was 5/6. Mean age was 64 y (55-76). There were 4 adenocarcinoma's, 3 T-cell lymphoma's, 2 Gist tumors, 1 case of multiple carcinoid tumors, and 1 hemangioperycitoma. The main indications for performing VCE were : intestinal bleeding of undefined origin or iron deficiency anemia (7), protein loosing enteropathy and malabsorption (2), episode of intestinal occlusion (1), abdominal lymphnodes on CT-scan (1). The mean number of diagnostic gastro-intestinal procedures before performing VCE was 3,6. Procedures before VCE were : oesophago-gastro-duodenoscopy (13), colonoscopy (11), SB series (8), CT-scan (4), and push enteroscopy (4). The localisations of the malignant lesions were : SB (5), jejunum (4), diffuse (2). The aspects of the lesions on VCE were :erosive or ulcerative lesions (6), tumor (4), active bleeding lesions (4), stenosis (2), vascular ectasia (1). In 8/11 cases (73 %), the VCE had a diret impact on the therapeutic decision that was in all cases surgery, becauseVCE was the only investigation able to detect the lesion. In 1 of these cases however, the lesion was detectable on CT-scan performed after VCE. The real direct impact of VCE on therapy was therefore 64 %. Seven of these 8 cases concerned bleedings or iron deficiency anemia. In the 2 cases of malabsorption, the VCE had no influence on therapy. In 1 case of vascular tumor, VCE was used for evaluating the extent of the lesion but had no impact on therapy.
Conclusion : VCE was able to detect a malignant SB lesion in 2,3 % of the procedures and had a direct impact on therapy in 64 % of these cases. Despite traditional endoscopic and radiological work-up, VCE was able to make a correct diagnosis and to influence directly therapy in 64 % of these patients. Tumors of the SB remain however a rare condition and VCE should only be performed in well-selected patients.

- D30 -

COLECTOMY RATES AFTER CYCLOSPORINE INDUCED REMISSION : 7 YEARS EXPERIENCE IN SEVERE ULCERATIVE COLITIS. B. Maenhout, D. Moskovitz, G. Van Assche, J. Arts, S. Vermeire, P. Rutgeerts. Division of Gastroenterology, University of Leuven.

Introduction. Cyclosporine A (CSA) has been shown to be effective in steroid refractory ulcerative colitis and as an alternative to glucocorticosteroids in patients with severe attacks of UC. While possessing clear short term benefits, the long term follow up of patients receiving CSA, beyond 3 years, is unknown. Our aim was to investigate the long term efficacy of CSA.
Methods. We performed a retrospective cohort study of all patients admitted to our institution with an attack of ulcerative colitis treated with IV CSA between Nov 1992 and Oct 2004. Patients received CSA at 4mg/kg or 2 mg/kg. Patients who responded to IV CSA were switched to Neoral for 3 months. CSA failure was defined both as a recurrence of symptoms as well as progression to colectomy. Kaplan Meier curves were used for survival analysis with quantitative variables compared using two-tailed student t test and qualitative variables compared with chi square analysis.
Results. Of the 142 patients, 65 (46 %) were female with a mean age of 41 years. 118 (83 %) of the 142 had an initial response to CSA and avoided colectomy during initial hospitalization. Of the 118 patients, 64 (54 %) required a future colectomy. For short and long term response, patients were similar with respect to age, disease duration, and duration of IV CSA. The rate of colectomy in those already on azathioprine compared to those starting azathioprine concurrently with CSA was 59 % vs 31 % respectively ($p < 0.05$). Also, 88% of patients already on azathioprine and requiring colectomy were operated within the first year of receiving CSA. Life table analysis shows that while only 33 % of patients require colectomy at 1 year, 88% will require colectomy at 7 years, Table.

Year	1	2	3	4	5	6	7
No. patients	129	81	68	51	41	27	14
Percent without colectomy	67	57	48	41	31	16	12
Percent in remission	41	35	25	18	12	8	6

Conclusions. CSA is an effective short term treatment for patients with severe ulcerative colitis but at 7 years 88% of patients will require a colectomy. Azathioprine naïve patients have better outcomes.

- D31 -

ASSOCIATION BETWEEN IGF1 GENE POLYMORPHISMS AND CROHN'S DISEASE PENETRATING BEHAVIOR. N. Boussif (1), C. Libioulle (1), J. Thys (2), J. Belaiche (2), R. Winkler (3), M. Malaise (4), M. Georges (1), E. Louis (3). (1)Laboratoire de génétique quantitative et factorielle, CBIG, ULg ; (2) Gastro Unit, CHU Liège ; (3) Laboratoire d'oncologie moléculaire, CBIG, ULg ; (4) CTCM, CBIG, ULg.

Crohn's disease (CD) behavior is characterized by the inclination to develop penetrating or stricturing complications over the disease's course. Genetic background may influence this behavior. Insulin-like Growth Factor 1 (IGF1) is involved in epithelial restitution, collagen deposition and smooth muscle cells hyperplasia. IGF1 is overexpressed in CD. The aim of our work was to study a series of SNP polymorphisms covering all the IGF1 gene to assess its association with CD behavior.
Patients and methods : we studied 371 CD patients with complete phenotype characteristics, 500 ethnically matched controls and 222 UC patients. CD behavior was defined 5 years after diagnostic in every patients, according to Vienna classification. Ten SNPs located across IGF1 gene were genotyped with the TaqMan technology for allelic discrimination (ABI). P values were corrected (Pc) for multiple tests (n = 20).
Results : No significant difference in genotype frequencies was found when comparing controls, UC and CD as a whole. When comparing the various CD behaviours, a significant difference was found for SNP located in intron 1 (+198) (Pc = 0.0144), SNP located in intron 3 (+13973) (Pc = 0.028) and SNP located in intron 3 (+30768) (Pc = 0.0148) (SNP intron 1/ intron 3 (+13973) /intron 3 (+30768) less frequent allele homozygotes : 5.1 %/7.8%/ 5.1 %, 3.0 %/3.1 %/3.0 %, 10.4 %/18.5 %/14.7 %, in nonstricturing nonpenetrating CD (n = 118), stricturing CD (n = 99), penetrating CD (n = 154), respectively). When comparing intraabdominal and perianal penetrating CD, no significant difference was found. Homozygocity for the less frequent allele of the SNP in intron 3 (+30768) gave a RR of 1.89 (1.44-2.49 ; p = 0.0007) for the development of a penetrating complication within 5 years after diagnostic.
Conclusion : we identified a group of 3 SNPs located in intron 1 and 3 of IGF1 gene, significantly associated with the development of early penetrating complications of CD.

- D32 -

VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) POLYMORPHISMS ARE IMPLICATED IN SUSCEPTIBILITY TO IBD. M. Ferrante, L. Henckaerts, T. Hlavaty, M. Pierik, M. Bueno de Mesquita, N. Van Schuerbeeck, G. Claessens, P. Rutgeerts, G. Van Assche, S. Vermeire. University Hospital Leuven, Department of Gastroenterology.

Background & Aim : Vascular endothelial growth factor VEGF is a potent angiogenic factor implicated in early wound healing and fibrosis. Increased serum levels (sVEGF) have been demonstrated in patients with Crohn's disease (CD) and ulcerative colitis (UC). VEGF production is significantly higher in fibroblasts isolated from strictures than from non-strictured segments in CD. Three variations in the VEGF promoter/leader sequence influence VEGF expression. We hypothesised that VEGF is a good candidate gene for IBD both from a functional as well as a positional (6p21, *IBD3* locus) perspective. Therefore, functional polymorphisms were studied in a cohort of IBD patients and correlated with sVEGF.
Methods : A cohort of 375 IBD trios (303CD/66UC/6IC) and 96 healthy ethnically matched controls were genotyped for C-2578A, G-1154A and G-634C in the VEGF promoter/leader sequence using DHPLC. TDT and Haplotype-TDT were performed using Genehunter 2.1. Individual haplotypes were calculated in PHASE 2.1 and correlated to sVEGF (ELISA).
Results : Mean sVEGF was higher in IBD patients compared to controls (439.4 vs 313.3 pg/ml, p = 0.002 unpaired t-test) and highest levels were seen in UC compared to CD (536.2 vs 414.0 pg/ml, p = 0.031). Of all 8 possible haplotypes, only 4 had a frequency > 1 % (CGG 16.3 %, CGC 33.1 %, AGG 18.6 % and AAG 30.5 %). The CGC haplotype was significantly undertransmitted in IBD (T:UT 75:106, p = 0.021) and most significant results were obtained in UC (T:UT 9 :25, p = 0.006). Interestingly, this haplotype was associated with lower sVEGF (399.8 ± 249.2 pg/ml) compared to the other haplotypes (615.1 ± 505.4 pg/ml, p = 0.058). In contrast, the AGG haplotype was more frequent in IBD and UC compared to controls (18.6 % and 23.4 % vs 11.2 %, p = 0.017 and p = 0.004 respectively), although no strong overtransmission could be documented (T:UT for UC 18 :10, p = 0.13). However, parallel to what was observed for the CGC haplotype and sVEGF, the AGG haplotype was associated with higher sVEGF (665.5 ± 538.8 pg/ml) compared to the other haplotypes (419.9 ± 289.6 pg/ml, p = 0.034). There was no association between haplotypes and extension of disease or need for colectomy. In CD, no association was seen between haplotype and sVEGF or phenotypic features.
Conclusions : We found that a CGC VEGF promotor haplotype was protective for UC, and that this haplotype was associated with lower serum VEGF levels. On the contrast, the AGG haplotype was more frequent in UC and associated with higher serum VEGF levels. We therefore conclude that VEGF seems implicated in susceptibility to IBD and more in particular, to UC.

- D33 -

LYMPHOTOXIN ALPHA HAPLOTYPES ARE NOT ASSOCIATED WITH CLINICAL OR BIOLOGICAL RESPONSE TO INFLIXIMAB IN CROHN'S DISEASE. V. Dideberg (1), E. Louis (2), F. Farnir (3), S. Vermeire (4), P. Rutgeerts (4), M. DeVos (6), A. VanGossum (7), J. Belaiche (2), V. Bours (1). (1) Human Genetic unit, CHU Liège ; (2) Gastro Unit, CHU Liège ; (3) Quantitative and factorial genetic, Liège University ; (4) Gastro Unit, Gasthuisberg Leuven ; (6) Gastro Unit, UZ Gent ; (7) Gastro Unit, Erasme Hospital Brussels.

Infliximab, a chimeric anti-tumor necrosis factor, is effective in the treatment of refractory luminal or fistulizing Crohn's disease (CD). An association between a lymphotoxin alpha (LTA) haplotype and the response to Infliximab in CD patients has been previously described in a relatively small cohort (1). This potentially clinically relevant association has not been confirmed or invalidated since then. Our **aim** was to study this association in a larger Caucasian cohort.

Patients and Methods : We studied by sequencing and fluorescent PCR the LTA haplotype (Nco1, TNFc, aa13L, aa60, as well as new SNP rs 3093543 and rs7468686) in a Caucasian cohort of 214 patients with either luminal (n = 150) or fistulising (n = 64) CD. Clinical response was defined as complete, partial or absent according to the same definition as in controlled trials. **Erreur ! Référence de lien hypertexte non valide.**

Results : Clinical response was complete, partial or absent in 45.8%, 19.6 % and 34.6 % of patients, respectively. Biological response was observed in 80.6 % of patients. No association was found between the previously published 1-1-1-1 haplotype and the response to Infliximab (clinical response : Fisher exact test, n = 214, p = 0,215 ; biological response : n = 139, p = 0,235). When the two other SNPs (rs 3093543 and rs7468686) were also included, the haplotypes comprising the six polymorphisms were not associated to clinical or biological response either. Likewise, no association was found between clinical or biological response to infliximab and individual SNPs studied separately. These negative results were obtained as well on the complete cohort, as separately on the luminal and fistulising CD.

Conclusions : We could not confirm an association between the LTA locus and clinical or biological response to Infliximab in our cohort of CD patients. Hence the size of our cohort is sufficient to exclude this association in Caucasian patients with a reasonable power.

1. Taylor *et al*. Gastroenterology 2001 ; 120 : 1347-1355.

- D34 -

FUNCTIONAL VARIANTS OF OCTN CATION TRANSPORTER GENE ARE ASSOCIATED WITH PERIANAL CROHN'S DISEASE. C. Libioulle (1), J. Thys (2), F. Farnir (1), O. Dewit (4), J. Belaiche (2), P. Mainguet (6), F. Mokaddem (7), F. Fontaine (8), J. Deflandre (9), H. Demolin (10), M. Georges (1), E. Louis (2). (1) Laboratoire de génétique quantitative et factorielle, CBIG, ULg ; (2) Gastro Unit, CHU Liège ; (4) Gastro Unit, Clinique St Luc, Brussels ; (6) Mons ; (7) Service de gastroentérologie, Hopital de l'Ardenne, Libramont ; (8) Service de gastroentérologie, St Joseph, Liège ; (9) Service de gastroentérologie, CHR citadelle, Liège ; (10) Service de gastroentérologie, Hopital civil de Verviers.

Introduction : Functional variants of the cation transporter genes, OCTN1 (L503F) and OCTN2 (-207G/C), were recently shown to be associated with Crohn disease (CD). Using anonymous SNP markers spanning the corresponding IBD5 locus, Armuzzi *et al*. (1) presented evidence suggesting that the association might be specific for a CD subtype, namely the perianal form. We herein test the association of L503F and -207G/C with clinical CD subtypes in a cohort of Belgian patients.

Patients and methods : We studied a cohort comprising 619 CD patients including 209 trios, 102 duos, and 308 singletons. Untransmitted parental chromosomes from the trios were used as controls in addition to a cohort of 87 ethnically matched controls. CD phenotypes were defined at diagnosis and after 5 years of disease evolution. Genotyping of the L503F and -207G/C SNPs was done using the 5' exonuclease assay (Taqman®) using an ABI-7900HT sequence detection system. Allelic frequencies in cases and controls were compared using a one-sided chi-squared test. Maximum likelihood haplotype frequencies were estimated using an EM algorithm.

Results : We found no evidence for an association of L503F and -207G/C with CD neither when considering each marker alone (p = 0.235 ; p = 0.113 respectively), nor when considering them jointly as a haplotype. However, when singling out patients suffering from perianal disease at the time of diagnosis (n = 72), the corresponding analysis yielded strong evidence for an association with both markers considered separately (p = 0.009 for L503F ; p = 0.011 for -207G/C) as well as jointly (p = 0.0025). The alleles associated with increased susceptibility were the same as those previously reported by Peltekova *et al*. (2). The association was also strongly present in the subgroup of CD patients developing perianal lesions within 5 years of disease evolution.

Conclusions : The OCTN cation transporter genes do not seem to be associated with CD as a whole in the Belgian population. However, we found a strong evidence for association with perianal CD, confirming and refining the association previously found between perianal CD and the IBD5 locus.

1. Armuzzi A, *et al*. Gut 2003, 52 : 1133.
2. Peltekova VD, *et al*. Nat. Genet. 2004, 36 : 471.

- D35-

STUDY ON DLG5 AND OCTN POLYMORPHISMS SHOWS ASSOCIATION OF THE OCTN TC RISK HAPLOTYPE WITH PERIANAL AND FISTULIZING CROHN'S DISEASE BUT NOT WITH SUSCEPTIBILITY TO IBD.
S. Vermeire, M. Pierik, L. Henckaerts, T. Hlavaty, M. Ferrante, M. Bueno de Mesquita, G. Claessens, N. Van Schuerbeeck, S. Joosens, R. Vlietinck, P. Rutgeerts. Leuven.

Introduction and Aims : Three years after the identification of NOD2/CARD15 two more genes for inflammatory bowel diseases (IBD) were reported. The carnitine/organic cation transporter (OCTN) cluster on 5q31 (*IBD5* locus) is associated with Crohn's disease (CD) and DLG5 (10q23), a member of the MAGUK (Membrane Associated Guanylate Kinase) family with IBD. Since both findings have not been replicated, and since it is not known if and to which extent mutations in these genes relate to disease phenotype, we studied mutation prevalence, phenotypic expression and gene-gene interactions.
Methods : A cohort of 2032 individuals was genotyped for the disease-associated OCTN (OCTN1 C1672T and OCTN2-207) and DLG5 variants (G113A and DLG5-e26). For the 981 IBD patients (CD = 769, UC = 186, IC = 26) all followed at a tertiary IBD-referral center phenotypes were available. The association study was performed with a 2 cohort approach : for 373 patients DNA of both parents was available for TDT (cohort1) and a second independent cohort (cohort 2) consisted of 608 patients and 305 controls.
Results : There was no distortion of transmission towards affected offspring for any of the variant alleles. Also case-control analysis failed to shown association for the studied variants. A higher frequency of the DLG5 113A allele was observed in CARD15+ (12.2 %) compared to CARD15- patients (8.7 % ; $p = 0.033$). In univariate analysis, OCTN2-207C was associated in a dose dependent manner with the presence of perianal disease (31.5 %, 35.1 % and 42.4 % for carriage of 0, 1 or 2 mutations respectively, $p = 0.038$) and the same trend, although not significant, was observed for OCTN1-1672T (33.9 %, 36 %, 42.5 % respectively, $p = 0.10$). In multivariate analysis, the OCTN TC-risk haplotype was associated with a fistulizing disease behavior (OR 1.47, 95 % CI 1.03-2.11 ; $p = 0.035$). For DLG5, there were no associations with a particular phenotype.
Conclusion : DLG5 and OCTN do not play a role in the susceptibility to IBD, CD or UC in our population but may play a role in the phenotypic expression of the disease. OCTN variants were associated with a perianal location and a fistulizing behavior of the disease and strengthen the reported association of the IBD5-risk haplotype with fistulizing disease. For DLG5, we confirmed the reported interaction with CARD15.

- D36 -

STUDY ON CARD15 AND TLR4 POLYMORPHISMS IN CHILDREN WITH EARLY DIAGNOSED IBD AND THEIR FAMILY MEMBERS.
M. Bueno de Mesquita (1), L. Henckaerts (1), M. Joossens (1), V. Janssens (2), T. Hlavaty (1), M. Ferrante (1), M. Pierik (1), M. Joossens (1), N. Van Schuerbeeck (1), G. Van Assche (1), S. Vermeire (1), I. Hoffman (1), P. Rutgeerts (1). (1)University Hospital Gasthuisberg, Department of Gastroenterology ; (2) University Hospital Gasthuisberg, Department of Pediatrics.

Background & Aims Genetic studies in adult IBD patients have highlighted associations with CARD15 and Toll Like Receptor (TLR) polymorphisms. These studies further suggest that variants influence disease location, behaviour and natural history. However, only few pediatric studies are available and only deal with CARD15. Therefore, we examined a large pediatric cohort of IBD patients and their family members for CARD15 and TLR4 mutations as well as for ASCA and pANCA.
Methods We collected 99 children with a diagnosis of IBD before the age of 17 followed at a tertiary referral center (CD = 80, UC = 16, IC = 3). We also included 335 first degree family members and 40 children without IBD (control group). All individuals were analysed for CARD15 R702W, G908R and L1007fs, for TLR4 Asp299Gly and for ASCA and pANCA. Clinical characteristics were examined at onset as well as at follow up.
Results Mean age at diagnosis was 11.9 ± 3.2 yr. Familial IBD was present in 32/99 (32 %) of patients. Besides traditional symptoms, 34 % of children presented with failure to thrive and 21 % with anemia. Most children (> 90 %) presented with an inflammatory behaviour at diagnosis, however, 35 % evolved towards stricturing and 32 % towards fistulising disease after a mean of 7.6 yr of follow-up. We observed a high frequency of CARD15 variants in CD (54 %), as compared to UC (19 %, $p = 0.01$) and controls (21.9 %, $p < 0.001$). Healthy relatives of CD patients had more often CARD15 variants (38.3 %) than controls ($p = 0.05$) but less than their affected CD relatives ($p = 0.007$) The TLR4 mutated allele frequency was 10.6 % in CD, compared to 0 % in UC and 5.3 % in controls ($p = 0.053$ and $p = 0.016$ resp) and was associated with less perianal disease (OR 0.76 95 % CI 0.61-0.95, $p = 0.076$). ASCA was present in 30 % of CD, compared to 7.1 % in UC ($p = 0.08$) and 7.1 % in controls ($p = 0.001$) and was associated with stricturing disease (OR 3.63 95 % CI 1.27-10.38, $p = 0.013$). For pANCA, prevalence was 40 % in UC compared to 6.8% in CD and 2 % in controls (all $p < 0.01$). A number of concomitant diseases were observed : 7 patients (all CD) had ankylosing spondylitis, 4 psoriasis, 10 asthma and 2 patients had Turners Syndrome (both CD).
Conclusions In this pediatric IBD cohort, frequency of CARD15 variants was as high as 54 % among CD patients and 38% among their healthy relatives. We also identified a higher frequency of TLR4 Asp299Gly polymorphisms among CD and for the first time report an inverse association of this SNP with perianal disease.

- D37 -

A RANDOMIZED PLACEBO-CONTROLLED CLINICAL TRIAL OF PROBIOTICS (L. JONHSONII, LA1®) ON EARLY ENDOSCOPIC RECURRENCE OF CROHN'S DISEASE (CD) AFTER ILEO-CAECAL RESECTION.

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RATIONALE : A 70 % of patients exhibit recurrent endoscopic lesions within 1 year demonstrating early and rapid relapse of intestinal inflammation after surgery. This study was designed to assess the effect of an oral administration of probiotics for preventing early post-operative recurrence of CD.
Patients and Methods : Patients with CD were pre-operatively enrolled when scheduled for ileocaecal resection and were randomly assigned after surgery to daily treatment of either L. jonhsonii La1®, Nestlé (1010 CFU) (group A) or a placebo (group B) for 12 weeks. No other medication was allowed during this study period.
Design : a multicenter, prospective, randomized, placebo-controlled clinical trial. Stratification was performed according to current smoking status at the time of randomization. All the data were considered in an intention-to-treat (ITT) model and a per-protocol (PP) analysis.
Objectives : The primary objective was to assess the effect of La1® on the endoscopic relapse rate (Rutgeerts score : i0 to i4) at week 12. The secondary objectives evaluated the histological score (Geboes score), clinical relapse rate (CDAI), serum CRP level, safety and tolerance.
Results : Seventy patients (33 females-37 males ; mean age at onset : 26 ± 9 years ; mean age at randomization : 37 ± 13 years ; 87 % suffering from a fibrostenotic disease (B2)) were enrolled with 34 patients assigned to group A and 36 to group B. The mean endoscopic score was not different between group A and group B at week 12 (1.44 ± 1.31 vs 1.05 ± 1.21, respectively ; NS). The percentage of patients with mild (i1+i2) or severe endoscopic recurrence (i3+i4) was not significantly different between the 2 groups (Mild : A = 45.2 % vs B = 39.3 %, NS ; severe : A = 27.9 % vs B = 33 %, NS). At week 12, there was no difference between the 2 groups for the following : histological score, CDAI and serum CRP level. The Pearson correlation coefficient between the histological and endoscopic score was equal to 0.496 (p = 0.0003). Forty-nine patients were considered in the PP analysis which showed similar results. Tolerance was similar in both groups. There was no serious adverse event probably related to the treatment in group A, but one in group B.
Conclusion :Oral administration of La1® in patients with CD failed to prevent early endoscopic recurrence at 12 weeks after ileo-caecal resection. No therapeutic gain was observed on histological score, clinical relapse or CRP level. Administration of La1® was considered to be safe.

- D38 -

PROTEOMIC USING SELDI-TOF-MS FOR THE DIAGNOSIS OF CROHN'S DISEASE AND ULCERATIVE COLITIS.

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The diagnosis of Crohn's disease (CD) and ulcerative colitis (UC), the two main inflammatory bowel diseases (IBD), still relies on invasive diagnostic tests including endoscopy and histology. The best blood markers, ANCA and ASCA have relatively good specificity (around 80 %) but rather low sensitivity (around 50 %), making them weak diagnostic tools. The aim of our work was to use sera protein profiling on SELDI-TOF (Surface Enhanced Laser Desorption-Ionization, Time of Flight Mass Spectrometry) to try and obtain relevant markers for the diagnosis of CD and UC.
Methods : We studied protein profiles obtained from four categories of patients : CD, UC, HC (healthy controls) and ID (other inflammatory diseases), with 30 individuals in each group. These protein profiles were assessed on two types of surfaces : CM10 and Q10. We analyzed results by means of two different statistical approaches : '*p Value'* determination on integrated peaks (each corresponding to some form of protein) and calculation of multiple decision trees ('*extra-trees'* or '*boosting'* methods) built on total data set as well as on integrated peaks.
Results : comparing IBD as a whole to HC and ID, decision trees gave a specificity of 88.8% on Q10 chips and 90.4 % on CM10 chips and a sensitivity of 82.9 % and 86.3 %, respectively. When CD was compared to the 3 other groups, we reached 95.8% and 92.8% specificity and 70.8% and 77.7 % of sensitivity on Q10 and CM10 respectively.When UC was compared to the 3 other groups, sensitivity was lower, around 40 %. Nevertheless, the specificity was still very good with 92.2 % on Q10 and 96.4 % on CM10 chips. When UC was compared to CD we obtained models with 80 % and 85 % specificity, while the sensitivities were 81.6 % and 90.8% on Q10 and CM10, respectively. The peaks occupying important places in the decision trees had also very significant *p Value* in individual analysis.
Conclusions : using two different surfaces to assess protein profiles, we obtainedtwo predictive models of classification which are around 80 % specific and sensitive. These models could lead, after cross validation and blind tests on new samples batches, to a very robust and easy-to-use diagnostic tool. Moreover, these models revealed many discriminating peaks and the downstream purification and identification of their associated protein could help us to better understand such diseases and to highlight new therapeutic targets.

APPENDECTOMY AND ULCERATIVE COLITIS, AN ASSOCIATION WITH A “NORTH-SOUTH” EUROPEAN GRADIENT ? M. Schapira, O. Descamps, A. Sibille, L. Verbrugghe, J. M Ghilain, J. M. Maisin, M. Moulart, J. Henrion. Hopital de Jolimont, Service Gastro, 7100 Haine St-Paul, Belgium.

Several studies have shown a protective effect of appendectomy on the incidence of ulcerative colitis (UC). The **aim** of this study was to test this hypothesis regarding the ethnic origin (Italian/Belgian) of our patients.
Methods : 90 UC patients (33 of Italian origin) were compared to 270 sex-and age-matched controls for their ethnic origin,their smoking habits and their history of appendectomy and tonsillectomy.
Results :Appendectomy was less frequently reported in UC-patients (16 % vs 35 %, OR : 0,34 ; 95 %CI : 0,18-0,63 ; p = 0,0004).,whilst tonsillectomy was reported with a similar prevalence (39 % in both groups). The current prevalence of smoking was similar beween UC-patients and controls,but past smoking status was more frequent in UC-patients (37 % vs 26 %,p = 0,004). The negative relationship between appendectomy and UC was more pronounced in the Italian population (OR: 0,18, p = 0,004)than in the Belgian population (OR : 0,47, p = 0,05).Indeed,in the Italian population, appendectomy was reported in 12 % of UC-patients and 42 % of controls, whereas the prevalence of appendectomy was 22 % and 35 % in Belgian UC-patients and Belgian controls,respectively. In a covariance analysis appendectomy (OR : 0.18 ; 95 % CI : 0,07-0,57,p = 0,006) and Belgian origin (OR : 0,26;95 % CI : 0,15-0,44 : p less than 0,001) were found to be independent risk factors for UC.
Conclusions : To our knowledge,this is the second case control study showing a protective effect of appendectomy for UC in our country. Our study indicates that this protective effect could be modulated by an ethnic (genetic ?) factor.

UPPER GI TRACT POSTERS

RADIOFREQUENCY DELIVERY (THE STRETTA PROCEDURE) REDUCES THE DISTENSIBILITY OF THE GASTRO-ESOPHAGEAL JUNCTION IN GERD PATIENTS. J. Arts (1), R. Vos (1), K. Gebruers (1), D. Sifrim (1), T. Lerut (5), P. Rutgeerts (1), J. Janssens (1), J. Tack (1). (1)Dept.of Gastroenterology,UZ Gasthuisberg, KU Leuven ; (5)Dept. of Thoracic Surgery, UZ Gasthuisberg, KU Leuven.

Introduction : Several publications, including one randomised double-blind sham-controlled study, have reported that radiofrequency delivery at the lower esophageal sphincter (LES) - the Stretta procedure - provides symptom relief in gastro-esophageal reflux disease (GERD). The mechanism underlying this improvement is unclear as pH monitoring and esophageal manometry did not show consistent changes. We hypothesized that the Stretta procedure would decrease the volume of the refluxate, which is not readily detected by pH monitoring, through a change in distensibility of the LES.
Objective : To evaluate the influence of Stretta procedure on symptoms, acid exposure and distensibility of the LES in GERD.
Methods : Seven GERD patients (6 females, mean age 51 ± 6) participated in the study. Before and 3 months after the Stretta procedure symptom score, pH-monitoring and LES distensibility were assessed. LES distensibility was assessed by positioning a barostat bag (max. 2.75x20 cm cylindrical shape) straddling the LES junction under fluoroscopy control. While the intrabag volume was monitored, stepwise isobaric distensions were performed with 2 mmHg increments at 30-second intervals until discomfort occurred. Distentions were repeated 20 minutes after administration of 50 mg of sildenafil, which served as a LES relaxant. Symptom severity and acid exposure were compared by Student’s t test. LES pressure/volume relationships were compared by 2-way ANOVA.
Results : Three months after the procedure, symptom score was significantly improved (18 ± 4 vs. 6 ± 2, $p < 0.05$) and esophageal acid exposure was not significantly decreased (18.3 ± 7 vs. 12.8 ± 6.0 %time, NS). LES distensibility was significantly decreased, which was reflected by a downward shift in pressure/volume relationship (ANOVA, $p < 0.05$), accompanied by a decreased LES compliance (16 ± 5 vs. 8 ± 2 ml/mmHg, $p = 0.1$) and a tendency for decreased area under the curve (944 ± 285 vs. 600 ± 221 ml*mmHg, NS). After sildenafil, the difference in distensibility was no longer present.
Conclusion : The Stretta procedure is associated with a decrease in distensibility of the gastro-esophageal junction. Additional studies in larger numbers of patients will be required to determine whether decreased LES distensibility, through a decrease of the refluxate volume during reflux events, is relevant to GERD symptom improvement and to the relative lack of improvement on pH monitoring after the Stretta procedure.

MECHANISMS ASSOCIATED WITH WEIGHT LOSS IN TERTIARY CARE FUNCTIONAL DYSPEPSIA PATIENTS. G. Karamanolis, P. Caenepeel, J. Arts, J. Janssens, J. Tack. Gatroenterolgy Department, UZ Gasthuisberg.

In tertiary care functional dyspepsia(FD)pts, weight loss(WL) has been suggested to be associated with impaired accommodation, visceral hypersensitivity,and gastroparesis.It is unclear which of these mechanisms is the predominant one.The aim of the study was to perform a multivariate analysis of mechanisms associated with WL in tertiary care FD.
Methods : 682 FD pts(455 women, mean age : 42yr) filled out a symptom questionnaire including the amount of WL(kg).H.pylori(HP) status was determined in 449 pts and solid and liquid gastric emptying was studied in 576 and 466 respectively. In 283pts a barostat was performed to assess sensitivity and accommodation.We studied the relationship between the presence of WL > 5 % of original body weight and the amount of WL and HP status, gastric emptying, accommodation, sensitivity and demographics using univariate and multivariate analysis. Data are given as mean ± SEM.Results : WL occurred in 359pts(53 %),was on average 4.4 ± 0.2kg,and was significantly correlated to solid emptying t1/2 ($r = 0.10, p = 0.012$) and to lower distending pressures at first perception ($r = 0.53, p < 0.0001$) and discomfort($r = 0.38, p < 0.0001$).WL > 5 % occurred in 296pts(43 %) ; it was associated to female sex (73 %vs62 %, $p = 0.007$) and younger age (39 ± 0.9vs43 ± 0.8yr, $p = 0.0004$).Pts withWL > 5 %had a lower discomfort threshold (8.5 ± 0.3vs10.3 ± 0.4mmHgaboveMDP,$p = 0.0004$), a higher solid emptying t1/2 102 ± 5vs91 ± 3.3min,$p = 0.04$),and the prevalence of hypersensitivity (87 %vs22 %, $p = 0.004$),and impaired accommodation was significantly higher(43 % vs30 %, $p = 0.03$) The prevalence of HP infection and of delayed emptying for solids or liquids did not differ in pts with or without WL > 5 %. Multivariate analysis revealed that WL > 5 % was associated with younger age and female gender(OR 2.48, 95 %CI 1.5-4.2 and 1.8,1.0-3.1, respectively)and with impaired accommodation and gastric hypersensitivity(OR 2.16, 95 %CI 1.2-4.0 and 1.96,1.1-3.5, respectively).
Conclusions : In tertiary care FD pts, WL is associated with female gender, young age, delayed solid emptying, hypersensitivity to distention, and impaired accommodation.Impaired accommodation and visceral hypersensitivity are the principal pathophysiological mechanisms associated with significant WL.

YIELD OF 24 HOUR ESOPHAGEAL PH MONITORING AND BILITEC MONITORING IN PATIENTS WITH PERSISTING SYMPTOMS ON PPI THERAPY. T. Vanuytsel, G. Karamanolis, J. Arts, D. Sifrim, P. Caenepeel, R. Bisschops, J. Janssens, J. Tack. Gastroenterology Department, UZ Gasthuisberg.

Current management algorithms propose pH monitoring under PPI in suspected GERD with insufficient treatment response, but recent observations challenge this approach because of its low yield. The aim of the present study was to perform an audit of the outcomes of pH monitoring under PPI therapy in our unit, and to study the yield of additional non-acid reflux monitoring.
Methods : All pH monitoring studies under anti-reflux therapy since 1997, with or without simultaneous Bilitec monitoring, were analysed. Correlations with PPI dose, demographics, symptom pattern and endoscopic findings were analysed using chi-square and Student t-test. Results : From 1997-2003, 353 patients (160 men, mean age 49.5 ± 0.8 years) underwent pH studies on PPI therapy (28% half, 67 % full, and 5 % double dose PPI) for persisting typical (56 %) or atypical (44 %) symptoms. Simultaneous intragastric pH monitoring in 91 patients revealed significantly better acid suppression under double dose PPI ($p < 0.03$). In 186 patients, simultaneous Bilitec monitoring was performed. PH monitoring on PPI was pathological in 107 patients(30 %). Pathological pH monitoring on PPI was associated with older age (51.9 ± 1.5vs.48.5 ± 0.9), lower PPI dose (31 % under half, 32 % under full, and 16 % under double dose), typical reflux symptoms (64 vs. 52 %), and a higher prevalence of persisting esophagitis (53 vs. 36 %) and of hiatal hernia (58 vs. 26 %). Bilitec monitoring on PPI therapy was pathological in 115 patients(62 %), of which 75(40 %) had normal pH monitoring. Adding Bilitec increased the diagnostic yield over pH monitoring alone, from 31 to 66 % on half dose ($p < 0.005$), from 32 to 63 % on full dose ($p < 0.001$), and from 16 to 38% on double dose PPI (NS). The symptom marker was used by 73 patients during pH monitoring and 40 patients during bilitec montoring, with a positive symptom index in respectively 21 % and 11 %.
Conclusions : The yield of pH monitoring during PPI therapy is relatively low, especially on double dose PPI. Adding Bilitec monitoring significantly increases the diagnostic yield of reflux monitoring under PPI therapy.

- D43 -

SURGICAL TREATMENT OF ESOPHAGEAL LEIOMYOMA, 10 YEARS OF EXPERIENCE IN THE ERA OF MINIMALLY INVASIVE SURGERY. F Meekers, P Nafteux, W Coosemans, G Decker, P De Leyn, D Van Raemdonck, A Lerut Department of Thoracic Surgery Kuleuven.

Leiomyoma is by far the most common benign esophageal tumor, arising from the muscularis propria of the esophagus. The indications for surgery are symptomatic disease, tumors greater than two centimeters, evidence of growth, and confirmation of pathology to exclude malignant degeneration. Classic surgical treatment has been enucleation via right or left thoracotomy. However, in the era of minimally invasive surgery, laparoscopy and thoracoscopy have been presented as alternatives to open surgery. From 1993 onwards we favoured a minimalLY invasive approach, with right thoracoscopy for proximal and mid esophageal tumors, left thoracoscopy for distal tumors and more recently also laparoscopy for tumors located at the gastro-esophageal junction. From 1993 onwards until 2003, 17 patients underwent surgical treatment for leiomyoma in our department. Overall 10 patiënts were treated minimally invasive. Seven were treated via thoracotomy. This included one conversion for dense adhesions and two esophageal resections for extensive leiomyomatosis. Four others were treated via thoracotomy because of the need for an antirefluxprocedure (Belsey Mark IV) (n = 2), the position of the tumor at the gastro-esophageal junction (nowadays treated by laparoscopy) in one patient and a Giant Leiomyoma in one other patient. There were no major complications and there was no mortality. As expected, patients treated with minimally invasive surgery suffered less postoperative pain, and could be mobilised earlier and were discharged earlier than patients undergoing a thoracotomy (mean hospital stay 6.6 days vs 9.1days).
Conclusion : In our experience thoracoscopic and laparoscopic enucleation of leiomyoma of the esophagus is feasible and safe. Although thoracotomy still has a place in selected cases, we recommend a minimally invasive approach as the treatment of choice because it offers a great comfort to the patients.

LARGE AND SMALL INTESTINE POSTERS

- D44 -

DISEASE PROFILE, SELECTION CRITERIA AND OUTCOME OF PATIENTS REFERRED TO INTESTINAL TRANSPLANTATION (ITX) : A CENTER EXPERIENCE. J. Pirenne, I. Hoffman, P. Ferdinande, W. Coosemans, R. Aerts, D. Monbaliu, M. Hiele, G. Van Assche, V. Janssens, R. Van Hee, P. Zachee, P. Rutgeerts, J. Janssens, J. Tack, F. Nevens, K. Geboes, N. Ectors, D. Vlasselaers, G. Veereman, J. Fevery, B. Maes, R. Lombaerts. Intestinal Transplant Center, K.U. Leuven.

Intestinal transplantation (Itx) has evolved from an experimental endeavour into a life-saving treatment for pediatric & adult patients with short-bowel and TPN-induced severe complications. In Europe -and in stark contrast with the US- the referral pattern to Itx is less standardized and fewer cases are performed/reported. To better characterize and bring new insight into the potential Itx activity in our region, we evaluated the disease profile, the selection process, and the outcome of short-bowel patients referred to Itx at our center. A multidisciplinary adult & pediatric Itx program was launched in 1998. Since then, a candidacy for Itx was formally discussed in 31 patients (9pediatrics/22 adults). Criteria for Itx listing included : a) irreversible intestinal failure ; b) life-threatening TPN-complications ; & c) sufficiently preserved condition to tolerate Itx (surgery-immunosuppression). Of these 31 patients, 11 were in ‘too good’ condition (potential for reversibility of bowel failure and/or no life-threatening complication) and their survival with conservative therapy is 100 % at last follow-up (1 received a liver Tx at another center). On the contrary, 4 were ‘too sick’ to tolerate Itx, and of them, 3 (75 %) rapidly succumbed (sepsis). 6 candidates from abroad were excluded (4 due to terminal/hopeless condition ; 2 to extra-intestinal carcinomatosis). Of the 31 initial patients, 10 (32 %) were deemed suitable for Itx : 2 females (56yo and 57yo, bowel resection-TPN liver-failure) are well 2 & 4yrs after liver/Itx ; a 2 yo boy with volvulus is recovering from a recent liver/Itx ; 1 neonate with volvulus in whom family had refused Itx succumbed shortly thereafter to sepsis ; a 53yo male with crohn/amyloidosis succumbed to pneumonia while waiting for kidney-Itx ; a 50yo female with acute/diffuse splanchnic ischemia rapidly succumbed to sepsis/MOF while being prepared for multivisceral transplant ; a 11mth yo boy with enterocolitis/liver failure succumbed to GI bleeding while being prepared for liver/Itx ; 3 patients are currently waiting {32yo male with crohn for Itx, 25yo female with pseudo-obstruction for Itx, and 51yo female with bowel resection-renal failure for kidney/Itx}.
Conclusion : 2 thirds of short-bowel patients referred to Itx do not fulfill the criteria (either ‘too-sick’ or ‘too-good’). In 1 third, Itx is indicated and is life-saving -when done in due time- whereas the survival without Itx (natural history) is very poor. These data validate the selection criteria used and justify wider application of Itx in this selected group. Itx is limited by an -unexpected- shortage of available grafts and it is therefore essential that intestinal donors are identified and referred to procurement organizations. More short-bowel patients could be saved by an Itx if they were referred before being too sick to tolerate surgery, immunosuppression, and an unavoidable waiting period.

- D45 -

C-REACTIVE PROTEIN GENE POLYMORPHISMS ARE NOT ASSOCIATED WITH BIOLOGICAL OR CLINICAL RESPONSE TO INFLIXIMAB IN CROHN'S DISEASE. S. Willot (1), S. Vermeire (2), M. Ohresser (1), P. Rutgeerts (2), G. Paintaud (1), J. Belaiche (3), M. De Vos (4), A. Van Gossum (5), J. Colombel (6), H. Watier (1), E. Louis (3). (1) ImmunoPharmacogenetics of therapeutic antibodies research group, University of Tours ; (2) Gastro Unit, Gasthuisberg, Leuven ; (3) Gastro Unit, CHU Liège ; (4) Gastro Unit, UZ Gent ; (5) Gastro Unit, Hopital Erasme, Brussels ; (6) Gastro Unit, CHU Lille.

Introduction : We recently showed an association between *FCGR3A V/F* polymorphism and the biological response (assessed on the basis of C-reactive protein (CRP) concentration decrease) to infliximab in Crohn's disease (CD). The clinical response to infliximab is also associated with CRP concentration before treatment. Because *CRP* and *FCGR3A* genes are located on the same 1q23 locus, we wanted to exclude a linkage disequilibrium between the two genes. We further studied the association between *CRP* polymorphisms and response to infliximab in CD patients.
Methods : *FCGR3A* (V/F) polymorphism and three *CRP* polymorphisms (- 717 G/A in the promoter, 1444 C/T and CRP4 A/G in the 3'UTR) were determined in 206 healthy blood donors and 189 CD patients (previously studied for *FCGR3A*) having received infliximab for either refractory luminal (n = 133) or fistulizing (n = 56) CD. Clinical response was defined as complete, partial or absent according to the same definition as in controlled trials. Biological response was assessed in 148 patients who had elevated CRP (> 2 × upper limit) before treatment and for whom CRP values were also available after treatment (4 weeks (luminal) or 10 weeks (fistulizing) after infliximab). A positive biological response was defined as a decrease in CRP of at least 25 %. *FCGR3A*-158V/F polymorphism was determined using an allele-specific PCR assay ; CRP polymorphisms were determined by PCR-RFLP assays.
Results : There was no linkage disequilibrium between *CRP* and *FCGR3A* neither in healthy donors nor in CD patients. 74.4 % and 77.7 % had a positive clinical and biological response to infliximab, respectively. Proportions of CD having a positive clinical or biological response were not statistically different among the various genotypes of the 717 G/A, 1444 C/T and CRP4 A/G polymorphisms. Median relative decrease in CRP were similar in various genotypes and CRP concentrations before treatment were not significantly influenced by *CRP* polymorphisms either.
Conclusion : There was no linkage disequilibrium between *CRP* and *FCGR3A* polymorphisms in controls and CD patients. *CRP* polymorphisms were not associated with clinical or biological response to infliximab nor with CRP concentrations before treatment.

- D46 -

A STOP CODON MUTATION IN THE TUCAN (CARD8,CARDINAL) GENE IS ASSOCIATED WITH LESS FAVORABLE OUTCOME TO INFLIXIMAB TREATMENT IN CROHNS DISEASE (CD). M. Pierik, T. Hlavaty, M. Joossens, L. Henckaerts, M. Ferrante, M. Noman, G. Van Assche, S. Vermeire, P. Rutgeerts. University Hospital Gasthuisberg, Division of Gastroenterology.

Introduction : The role of TNF- ± in mucosal inflammation in CD is evident from clinical and animal studies and underlined by the effectiveness of TNF blocking agents in the treatment of CD. Inappropriate T cell apoptosis plays a role in the pathogenesis of CD and mounting evidence suggests that antibodies against TNF- ± (infliximab) have a pro-apoptotic effect on T cells and reduce Th1 cytokines. TUCAN plays a role in apoptosis and suppresses NF-ºB-regulated overexpression of TNF-receptors and cytokine production. An T to A substitution in TUCAN resulting in a stop codon was recently identified to be associated with CD.
Methods & Aim :Since TUCAN plays a role both in apoptosis as well as in NF-kB signalling and TNF response we hypothesized that a relationship may exist between this stop codon variant and response to infliximab. We genotyped 151 CD patients treated with infliximab for luminal (n = 108) or fistulizing (n = 42) disease for TUCAN C10* using MALDI-TOF and assessed clinical response (based on DCDAI) at 4 (luminal) or 10 (fistulizing) weeks following treatment.
Results :Clinical response was seen in 70.1 % of patients (68.5 % for luminal and 76.2 % for fistulizing CD) with remission obtained in 52.4 % of patients. In patients with luminal disease, the presence of a T allele was associated with higher response rates (41/50, 82 %) compared to patients homozygous for AA (31/55, 56.4 %) (OR 3.33 95 % CI{1.32,8.37}, p = 0.011). Also complete remission was significantly lower (38%) in patients homozygous for the AA genotype compared to patients carrying TT or TA genotypes (68%, p = 0.002) The response rates for all observed genotypes were higher in patients on concomitant Azathioprine (n = 46), however still remained significantly lower in patients with the AA genotype compared to patients carrying a T allele (61.9 % and 92 % respectively p = 0.014). For fistulizing disease, no differences were observed.
Conclusion :We found a less favourable outcome to infliximab treatment in patients with luminal CD who are homozygous for a stop codon allele at aa position 10 in TUCAN. Response as well as remission rates were significantly higher in patients carrying at least one copy of the TUCAN allele coding for a full-length protein. These data give evidence that the TUCAN C10* polymorphism may have important functional consequences and influence NF-ºB signalling and apoptosis leading to the observed alterations in infliximab response.

- D47 -

NATURAL HISTORY OF ILEAL CROHN'S DISEASE TREATED WITH STEROIDS. V. Bernard, J. Belaiche, E. Louis. Gastro Unit, CHU Liège.

Introduction : Steroid treatment is effective for inducing clinical remission in patients with ileal Crohn's disease (CD). However the impact of such treatment on the natural history of the disease in these patients, particularly the need for subsequent surgical resection has not been adequately studied. Our aim was to assess the steroid dependence, the need for surgery and the proportion of patients developing penetrating lesions, in CD patients with pure ileal disease, treated with steroids.
Methods : we identified in our database, the patients with pure ileal disease (L1 in Vienna classification) and non penetrating behaviour at diagnosis. We retrospectively reviewed the medical notes of these patients and recorded medical treatments, evolution of CD behaviour (penetrating B3, stricturing B2 or non penetrating non stricturing B1 according to Vienna classification) and the surgical resections.
Results : we identified 94 L1 patients, who were B1 or B2 at diagnosis and for whom, we had a complete clinical history in our medical notes. Median age at diagnosis was 25 yrs (11-79), there were 63 females, 84 were B1 and 10 B2 at diagnosis. The median follow up of these patients after diagnosis was 51 months (1-264). Among them, 62 have been treated with steroids. 11/62 (17.7 %) became steroid dependent and 6 (9.7 %) were treated with immunosuppressive drug (IS). The majority (46/62-74.2 %) of these steroid treated patients had to undergo surgical resection of the terminal ileum a median of 12 months (0.5-240) after initiating steroid treatment and 45 months (1-240) after diagnosis. In the non steroid treated patients, 2/32 (6.3 %) were treated with IS, and 17/32 (53 %) had to undergo surgical resection a median of 60 months (6-216) after diagnosis. Globally, in steroid treated patients, the median follow up in patients undergoing surgery was 44 months (1-240) as compared to 55 months (6-264) in non surgery patients ; there was no significant difference in smoking status, but significantly more patients had been treated with IS in the group of patients not needing surgery (25 % vs 4.3 % ; $p = 0.03$). The reason for surgery was the development of a penetrating ileal disease in 25/46 patients (54.3 %) while such penetrating complications were present in only 5/17 (29.4 %) patients not treated with steroids and who also required surgical resection ($p = 0.09$).
Conclusions : In ileal CD patients, steroid treatment does not seem to suppress the need for early surgical resection in most cases, although co-traitment with IS may lower this risk. The reason for surgery tends to be more often a penetrating disease in steroid treated patients than in others.

- D48 -

EVOLUTION OF THE PREVALENCE AND CHARACTERISTICS OF ANEMIA IN INFLAMMATORY BOWEL DISEASES OVER THE LAST 10 YEARS. A. Vijverman, P. Piront, J. Belaiche, E. Louis. Gastro Unit, CHU Liège.

Introduction : Anemia has been considered as an overlooked complication of inflammatory bowel disease (IBD). Studies dating back to the 80ties and the 90ties have shown 30 % of anemia among IBD patients. More recently, the broader use of immunosuppressive drug (IS) and infliximab allowing better mucosal healing as well as a more aggressive treatment of anemia, including the use of safer form of IV iron, may have influenced the prevalence of anemia among IBD patients. Our aim was to asses the prevalence and characteristics of anemia among two cohorts of IBD patients at 10 years interval and to look for associated clinical or demographic factors.
Methods : using the IBD patients register of one senior gastroenterologist (JB) we identified IBD patients he had consecutively seen and who had blood test at the outpatient clinic during the years 1993 and 2003. Demographic and clinical characteristics, treatment for IBD, blood test results and treatment of anemia were recorded and compared between these two cohorts. Anemia was defined as an hemoglobin level lower than the normal value of the laboratory of our hospital.
Results : 80 and 90 patients were identified in 1993 and 2003, respectively. There was no significant difference between the two cohorts, according to age, gender, disease type, duration or location. There were 27/80 (33.8%) and 15/90 (16.7 %) anemic patients in 1993 and 2003, respectively ($p = 0.03$). The prevalence of severe anemia (hemoglobin level < 10.5 g/100ml) was similar in the two cohorts (6.3 % and 5.6 %). Characteristics of the anemia were similar in the two cohorts with a majority of iron deficiency anemia and inflammatory anemia. Ferritin and CRP levels were not significantly different in the two cohorts. The only significant difference was a more frequent use of IS in 2003 than in 1993 (32.2 % vs 15 %, $p = 0.007$, RR :0.46, 0.25-0.83).
Conclusions : Prevalence of mild to moderate anemia has significantly decreased in our population over the last 10 years. The only difference detected between the two cohorts was the increased use of IS (mainly azathioprine).

- D49 -

RETROSPECTIVE STUDY OF 21 PATIENTS TREATED BY HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY AND CYTOREDUCTIVE SURGERY FOR PERITONEAL CARCINOMATOSIS OF COLORECTAL ORIGIN. A. Rouers, S. Laurent, B. Detroz, M. Meurisse. CHU Liège.

Backgrounds : Peritoneal carcinomatosis (PC) from colo-rectal cancer 'signifies' a very poor prognosis with a mean and median overall survival times of 6.9 and 5.2 months. A locoregional therapeutic approach of this disease has been advocated and studies described that cytoreduction followed by hyperthermic intraperitoneal chemotherapy (HIPEC) improved survival of these patients. However, this combined treatment presents a high complication rate.
Methods : We performed HIPEC (Sugarbaker's Colliseum technique) combined to complete cytoreduction surgery in 21 patients presenting PC of colorectal origin. For each case the medical file was retrospectively analysed to determine feasibility, morbidity, mortality, survival time and prognostic factors.
Results : Pathological examination of the resected tumours revealed a UICC staging of II in 4 patients, III in 7 patients and IV in 10. The mean operating time was 453 minutes. After a median follow-up of 24.9 months, cancer recurrence was detected in 8 patients (38.0 %). The median survival time was 34 months. We noticed a morbidity rate of 33.3 % and one patient died two months after treatment (endocarditis).
Conclusions : This series seems to confirm positive impact of cytoreduction and HIPEC on PC. We obtained a moderated complications rate comparable to the literature data. These good results could be secondary to high degree of selection of the patient admissible to the technique.

- D50 -

GENE EXPRESSION PROFILE OF FOLLICLE ASSOCIATED EPITHELIUM COMPARED TO VILLUS EPITHELIUM. P. Verbrugghe, P. Demetter, J. Vandesompele, W. Waelput, C. Cuvelier. Dept. Pathology, University Hospital Ghent.

Introduction : The follicle associated epithelium (FAE) overlying the lymphoid follicles of Peyer's patches mediates transcytosis of antigens to the underlying lymphoid tissue, mainly by the presence of M-cells. So far, the molecular and biochemical characterization of the FAE and M-cells is at an early stage and few specialized M-cell specific characteristics are known.
Aims & Methods : In order to identifynew molecules important for FAE function, the gene expression profile of FAE was compared to that of villus epithelium (VE). Therefore, epithelium was isolated from murine Peyer's patch intestine and non-Peyer's patch intestine. Agilent Mouse Development Oligo Micrarrays were used to obtain a broad picture of differences in gene expression between FAE and VE. To confirm FAE specific expression of candidate genes, Q-PCR was performed.
Results : After microarray analysis and Q-PCR, significant differences (in a range of 2-fold to 10-fold) between FAE and VE were detected for the expression profile of 15 genes. These included genes encoding adhesion molecules (CD44, Srb-1), cytokines (macrophage migration inhibitory factor) and cytoskeleton molecules (tubulin beta 5).
Conclusion : A detailed knowledge of the FAE and in particular the M-cell phenotype is currently lacking. This study contributes to a better characterization of the FAE phenotype. In a next phase, immunohistochemistry and electron microscopy will be performed to detect M-cell specific molecules.

- D51 -

COLORECTAL STUMP AS A MAJOR RISK FOR COLORECTAL CANCER IN CROHN''S DISEASE. I. Bueres Dominguez (1), C. Sempoux (2), R. Fiasse (1), R. Detry (3), A. Geubel (1), O. Dewit (1). (1) Gastroenterology ; (2) Pathology ; (3) Colorectal Surgery UCL St Luc.

Background and aim : in Crohn's colitis and ulcerative colitis, screening for dysplasia and/or colorectal cancer (CCR) is advocated for diseases of 8 to 10 years duration. In addition, colon exclusion with stomy may be required in emergency surgical management of Crohn's disease (CD) but dysplasia and CCR have been only rarely described in patients with longstanding colorectal stump. We report the cases of 2 patients who developed a few years after surgery three CCR in the excluded colorectal stump.
Patient 1 is a 80-year-old man with CD for 5 years complicated by ileo-sigmoido-vesical fistulae that required a right hemicolectomy, sigmoidectomy and transverse colostomy. No follow-up was done because of the lack of compliance. He remained asymptomatic during 5 years under sulfasalazine therapy. After 5 years he exhibited hematochezia. A flexible endoscopy showed a rectal tumor of 9 cm in diameter and biopsies showed a picture of a poorly differentiated adenocarcinoma with transmural invasion and signet ring cells. A few days later the patient unfortunately died of pneumopathy prior to surgery.
Patient 2 is a 88-year-old man with Crohn's disease since the age of 28, time of his first ileocolonic resection. Forthy-five years later, due to the presence of several colonic and rectal benign stenosis, an ileostomy was performed. He was then lost for follow-up. Fifteen years after the ileostomy, he presented with hematochezia and the coloscopy showed two different tumors : one in the upper part of the rectum and another one 15 cm above the rectosigmoid junction. A colectomy was peformed and confirmed the existence of two separate cancers (both mucoid adenocarcinomas T3N0). Interestingly the whole colonic mucosa showed mild to severe dysplasia. The patient died 3 years later.
Conclusion These caricatural cases outline the high CCR risk in patients with colorectal stump ; the latest representing another risk group additive to that of patients with other risk factors such as cholangitis or familial history of intestinal neoplasia. The diagnosis is unfortunately often delayed because of the screening difficulties in these asymptomatic patients. In patients with colorectal stumps, coloproctectomy should be performed if reanastomosis is no longer considered. A second choice strategy should include an annual or biannual endoscopic surveillance with multiple biopsies to guide the decision of proctectomy.

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LONG TERM ADMINISTRATION OF LACTULOSE CAN STIMULATE BIFIDOBACTERIUM ADOLESCENTIS IN VIVO AND INFLUENCE THE COLONIC UREA-NITROGEN METABOLISM. V. De Preter (1), T. Coopmans (1), T. Vanhoutte (2), G. Huys (2), J. Swings (2), P. Rutgeerts (1), K. Verbeke (1). (1) University Hospital Gasthuisberg, KULeuven, Belgium ; (2) Laboratory of Microbiology, Ghent University, Belgium.

Introduction : Long-term dietary intervention with prebiotics causes changes in the relative populations of colonic bacteria and hence in microbial metabolic activities. In the present study the influence of lactulose on the composition of the intestinal microbiota was studied. Changes in metabolic activity, especially the metabolic fate of ammonia was investigated by means of lactose-[^{15}N, ^{15}N]-ureide (LU).
Methods : The effect of lactulose on the colonic fate of LU was evaluated in a randomized, cross-over study. At the start of the study and at the end of the 4-week treatment period the healthy volunteer consumed a test meal containing 75 mg LU. During the study period, the volunteers (n = 29) received 10g lactulose (b.i.d.). Urine was collected in different fractions during 48h and faeces during 72h. The bacterial fraction was isolated from the total faecal samples. All samples were analysed for ^{15}N-content by combustion-IRMS and results were expressed as % of administered dose. The 15N excretion in the bacterial fraction was expressed in ng/mg. A culture-independent approach using PCR-DGGE population fingerprinting was applied to determine the composition of the predominant faecal microbiota, using a universal primer targeting the V3 region of the 16S rRNA gene.
Results : After lactulose intake, a significant decrease in ^{15}N content was found, as compared to the baseline values, in the 6-24h urine fraction (from 2.31 ± 0.77 to 1.67 ± 0.61 ; p = 0.00016). No changes were observed in the 24-48h urine fraction. At the same time, significantly more 15N was found in the 72h faeces collection (from 4.68 ± 1.94 to 6.25 ± 2.21 ; p = 0.032). Analysis of the bacterial fraction demonstrated a significant increase of 15N after lactulose intake (from 8.06 ± 2.35 to 12.81 ± 5.82 ; p = 0.02). Comparison of DGGE banding patterns indicated the appearance or intensification of a specific DGGE band after lactulose intake, which was tentatively assigned to bifidobacterial organisms. Band sequence analysis showed that in 90 % of the cases, this band represented *Bifidobacterium adolescentis*.
Conclusions : Long-term administration of lactulose resulted in a common variation in DGGE profiles of human faecal samples which could be ascribed to a change in the *Bifidobacterium* population and more specifically to *Bifidobacterium adolescentis*. Collectively, our data indicate that dietary addition of lactulose can exert a bifidogenic effect accompagnied by a favourable effect on the colonic NH3-metabolism.

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EFFECTS OF LONG-TERM ADMINISTRATION OF LACTULOSE AND SACCHAROMYCES BOULARDII CELLS ON SERUM LIPIDS IN HEALTHY VOLUNTEERS. V. De Preter, T. Coopmans, P. Rutgeerts, K. Verbeke. Department of Gastrointestinal Research, University Hospital Gasthuisberg, KULeuven, Belgium.

Introduction : The emerging public consensus of the relationship between serum cholesterol and the risk of developing coronary heart disease and also of inducing colon cancer in addition to high dietary fat and low fiber, has resulted in an enhanced interest in those products to which cholesterol lowering properties are attributed. Non-digestible dietary carbohydrates, i.e. prebiotics, and probiotic strains are of specific interest. *In vitro* studies have demonstrated hypocholesteric properties of these substrates, but studies of the effects of pre- and probiotics on serum lipids in humans are until now inconsistent.
Methods : In this study**,** the effects of two different doses of lactulose and *Saccharomyces boulardii* cells on serum lipids were evaluated in a randomized, placebo-controlled cross-over study with 28 normolipidaemic persons. At the start of the study and at the end of each 4-week study period, during which they were treated with either a prebiotic (group 1 (n = 14) : 10g lactulose b.i.d. and group 2 (n = 14) : 15g lactulose b.i.d.), a placebo, or a probiotic (group 1 : 2 × 250mg *S. boulardii* cells per day and group 2 : 4 × 250mg *S. boulardii* cells per day), serum samples were taken and analyzed for total cholesterol, triglycerides and high-density lipoprotein (HDL) cholesterol content. Low-density lipoprotein (LDL) cholesterol was calculated. Statistical evaluation of the data was performed by applying the analysis of variances (ANOVA), including the Tukey test for differences.
Results : As compared with the pretreatment values, no significant differences were found for total cholesterol, triglycerides, HDL and LDL content in group 1 after administration of 10g lactulose or 250 mg *S. boulardii* cells twice a day. Neither did a higher dose of either the pre- or probiotic in group 2 did result in a significant difference.
Conclusions : Our results demonstrate that long-term administration of the substrates and a difference in dosage of lactulose or *S. boulardii* cells do not influence serum lipids in normolipidaemic individuals.

	mg/dl	Pretreatment	After prebiotic treatment	Placebo treatment	After probiotic treatment	p-value
Group 1 (n = 14)	Total cholesterol	175 ± 33	178 ± 35	178 ± 27	178 ± 26	NS
	Triglycerides	98 ± 21	85 ± 33	96 ± 36	89 ± 30	NS
	HDL	66 ± 5	69 ± 24	66 ± 18	62 ± 18	NS
	LDL	89 ± 30	92 ± 29	92 ± 21	95 ± 26	NS
Group 2 (n = 14)	Total cholesterol	181 ± 31	177 ± 20	170 ± 33	172 ± 33	NS
	Triglycerides	66 ± 22	75 ± 31	77 ± 31	77 ± 36	NS
	HDL	71 ± 7	63 ± 6	63 ± 12	64 ± 19	NS
	LDL	96 ± 29	90 ± 39	95 ± 30	95 ± 30	NS

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DIFFERENTIAL EFFECT OF INULIN AND LACTULOSE ON THE COLONIC NH3-METABOLISM EVALUATED USING A STABLE ISOTOPE BIOMARKER. V. De Preter, K. Geboes, T. Coopmans, P. Rutgeerts, K. Verbeke. Department of Gastrointestinal Research, University Hospital Gasthuisberg, KULeuven, Belgium.

Introduction : The accumulation of ammonia in the colon has been implicated in the pathogenesis of certain diseases and can be decreased by administration of non-digestible carbohydrates, as shown in *in vitro* studies. To compare the short- and long-term effects of the disaccharide lactulose and the non-starch polysaccharide Raftilin HP (> 99 % inulin) on the colonic fate of NH3 in healthy volunteers, the lactose-[^{15}N, ^{15}N]-ureide biomarker (LU) was applied in this study.
Methods : In order to evaluate the immediate influence of simultaneous administration of lactulose or Raftilin HP on the excretion of the labelled marker, the volunteers received a pancake test meal labelled with 75 mg LU to which in the first test no substrate and in the second test respectively 10g lactulose (n = 29) or 5g Raftilin HP (n = 12) was added. To study the influence of long-term administration (1 month) of the substrates, the volunteers consumed a 15N-labelled pancake test meal once before the start of the intake period and once again at the end. During the treatment period the volunteers received either 2 × 10 g/d lactulose (n = 29) or 3 × 5 g/d Raftilin HP (n = 7). For each test, the volunteers performed a 24h urine collection. ^{15}N-excretion was expressed as % of administered dose.
Results : The inclusion of inulin or lactulose into the test meal resulted in a decreased excretion of ^{15}N (p = 0.02, respectively p < 0.0001).

Short-term effects	Cum % of ^{15}N recovered over 24h		
	Baseline	Inclusion	p-value
Raftilin HP (n = 12)	55.63 (44.84-58.30)	41.40 (35.42-42.21)	0.02
Lactulose (n = 29)	33.26 (12.91-52.01)	19.09 (3.66-33.41)	< 0.0001

Long-term dietary intervention with inulin did not cause changes in the fate of labelled ammonia, whereas after 1 month lactulose intake, a significant decrease in % ^{15}N was found compared to baseline values (p = 0.006).

Long-term effects	Cum % of ^{15}N recovered over 24h		
	Baseline	Inclusion	p-value
Raftilin HP (n = 7)	53.61 (41.51-57.21)	52.02 (42.70-54.62)	NS
Lactulose (n = 29)	33.26 (12.91-52.01)	26.73 (3.67-47.37)	0.006

Conclusions : The results of this study demonstrate that simultaneous administration of lactulose or Raftilin HP decreases the urinary ^{15}N output. Long-term administration of lactulose also decreases urinary ^{15}N output whereas no prolonged effect was seen with Raftilin HP, which might be due to a stronger bifidogenic effect of lactulose as compared to long chain inulin.

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THE LOW GI OF CEREAL PRODUCT IS NOT DUE TO A LOWER GUT TRANSIT TIME BUT DUE TO SLOW RELEASE OF CARBOHYDRATE. K. Verbeke (1), V. De Preter (1), V. Lang (2), S. Vinoy (2). (1) Dpt Gastrointestinal Research, UZ Gasthuisberg, K.U.Leuven ; (2) Danone Vitapole, Palaisseau, France.

In recent years, the importance of low glycemic index (GI) food has generally been recognized, especially in relation to obesity and type II diabetes. The processing of cereal products has been shown to dramatically modify the digestibility of starch and thus the GI of products. The purpose of this study was to evaluate the effect of processing on the GI and the insulinemic index (II) linked to the transit time in the gut. Two model breakfast foods (plain biscuits and extruded cereals) with respectively high content of slowly available glucose (SAG = 23g/100g) and low content of SAG (1g/100g) have been developed and evaluated in vivo. Both foods had the same macronutrient composition (67 % carbohydrate, 8% protein, 25 % lipids). The GI and II was assessed in 12 healthy volunteers according to the WHO recommendations. In parallel, the gastric emptying and orocaecal transit time (OCTT) have been determined in 11 healthy volunteers using dedicated breath tests, with both model foods containing ^{13}C-octanoic acid and lactose ^{13}C-ureide. The GI of the plain biscuits and extruded cereals was respectively 41 ± 5 and 69 ± 12 (p = 0.05), and the II was respectively 60 ± 7 and 71 ± 8. Gastric half emptying time of the ^{13}C-labeled cereals and biscuits was not significantly different (81 ± 17 min vs 80 ± 26 min), neither was the OCTT (367 ± 81 min vs 355 ± 77 min). Although the macronutrient composition was identical, a significant difference in GI between both products was obtained. The lower GI of the plain biscuits based on a high content of SAG was not due to a delayed gastric emptying but most probably to a slower small intestinal digestion. Such low GI food based on slowly digestible starch, which tended to decrease the postprandial hyperinsulinemia could be of significant value in the prevention of obesity and diabetes.

RESISTANT STARCH INFLUENCES THE COLONIC AMMONIA METABOLISM BUT NOT THE PROTEIN FERMENTATION. K. Verbeke, V. De Preter, J. De Loor, P. Rutgeerts. Dpt Gastrointestinal Research, UZ Gasthuisberg, K.U.Leuven.

Introduction : The effects of resistant starch (RS) in the colon are mainly attributed to the generation of short-chain fatty acids and especially butyric acid. In this study, we have investigated whether RS also influences other colonic metabolic pathways, particularly protein fermentation and the ammonia metabolism. Lactose [^{15}N, $^{15}N'$]-ureide was used as a biomarker to evaluate the fate of colonic ammonia whereas the urinary concentration of p-cresol was considered as a marker of protein fermentation in the colon ([1]).
Methods : In order to evaluate the effect of RS administration, 10 healthy volunteers consumed three times a pancake test meal labeled with 75mg lactose [^{15}N, $^{15}N'$]-ureide, respectively as such, supplemented with placebo or supplemented with 15 g RS type 3, after which they performed a 48-h urine collection. Urinary ^{15}N content was measured using total combustion-IRMS and expressed as % of administered dose and the urinary p-cresol excretion was determined using GC-MS and expressed as total p-cresol content (mg).
Results : At baseline, 39.8 ± 17.1 % of administered 15N was recovered in the urine. Administration of RS resulted in a decrease with 8.8% (up to 31.0 ± 12.9 %) which was significantly different ($p = 0.023$) from the effect of placebo (increase with 1.2 % up to 41.0 ± 11.2 %). On the other hand, p-cresol excretion at baseline (36.7 ± 18.5 mg) was not significantly different from the excretion after administration of RS (37.7 ± 21.6 mg) or placebo (38.8 ± 20.0 mg).
Conclusions : It was found that administration of RS type 3 resulted in a decreased urinary excretion of 15N, indicating that either a lower amount of ammonia was generated in the colon or that a higher amount was removed through bacterial incorporation followed by faecal excretion. On the contrary, no influence on the protein metabolism was observed.

1 De Preter V *et al*. Br. J. Nutr. 2004 ; 92 : 439-446.

COULD 13C AND 15N LACTOSE UREIDE BE USEFUL BIOMARKERS TO CHARACTERIZE THE METABOLISM OF INTESTINAL BACTERIA IN CHILDREN ? S. Staelens (1), G. Veereman (1), V. De Preter (2), Y. Ghoos (2), K. Verbeke (2). (1) Queen Paola Children's Hospital-ZNA-Antwerp-Belgium ; (2) Department of Gastrointestinal Research, University Hospital Gasthuisberg, K.U.Leuven.

The ^{13}C lactose ureide (LU) test is a non-invasive, reliable method to assess orocaecal transit time (OCTT) in children. Expired $^{13}CO_2$ indicates the hydrolysis of ^{13}C LU by intestinal flora(1). ^{15}N LU is a biomarker for the evaluation of the ammonia metabolism in healthy adults. Urinary ^{15}N excretion indicates the accumulation of ammonia (2). Our aim is to assess whether ^{13}C & ^{15}N LU reveals changes in the ammonia metabolism of children, in health and disease. As a first step we studied the metabolization of ^{13}C&^{15}N LU in a group of 12 healthy children (6 girls) with a mean age of 9 yrs (range 6-12 yrs). Informed consents were obtained from the legal representatives and assent from the children. Subjects ingested 500 mg unlabeled LU the evening prior to the test. After an overnight fast 2 basal breath and a urine sample were taken. The testmeal consisted of a pancake labeled with 250 mg ^{13}C LU and 75 mg ^{15}N LU. Breath was sampled every 15 min during 10 hrs and analysedusing isotope ratio mass spectrometry (IRMS). Urinary fractions (0-6 hrs, 6-24 hrs, 24-48 hrs) were collected and analysedby combustion IRMS. Their ^{15}N content was expressed in percentage of the administered dose. $^{13}CO_2$ expiration yielded mean OCTT values of 278+/-65 min. The % dose ^{15}N excretion was 8,04+/-3,06 in the urine collection from 0-6hrs, 36,13+/-12,38 from 6-24hrs, 8,16+/-3,57 from 24-48hrs. The cumulative fraction from 6-48 hrs had a % dose 15N recovery of 44,28+/-12,13. 13C & 15N LU are metabolized by the intestinal flora of healthy children. The obtained values are comparable to reference values for OCTT in a similar pediatric studygroup([1]) and ^{15}N urinary excretion in adults([2]). ^{13}C & ^{15}N LU are potentialy useful biomarkers to unmask changes in colonic ammonia metabolism in children, induced by illness or functional foods.

(1) Van Den Driessche *et al*., J. Pediatr. Gastroenterol. Nutr. 1997 ; 25 : 483
(2) De Preter *et al*.,Br. J. Nutr. 2004 ; 92(3) : 439-46

MORPHOLOGICAL STUDY OF INTERLEUKIN-10 PRODUCING LACTOCOCCUS LACTIS IN MOUSE ILEAL LOOPS. A. Waeytens (1), S. Neirynck (2), W. Waelput (1), P. Rottiers (3), L. Steidler (2), C. Cuvelier (1). (1) Pathology, Ghent University, De Pintelaan 185, 9000 Ghent, Belgium ; (2) Alimentary Pharmabiotic Centre, University College Cork, Western Road, Cork, Ireland ; (3) Molecular and Biomedical Research, Ghent University - VIB, Technologiepark 927, 9052 Zwijnaarde, Belgium.

Objectives : *Lactococcus lactis* is a non-invasive, non-pathogenic gram-positive bacterium, extensively used in dairy industry. Steidler *et al.* (2000) demonstrated that treatment of murine colitis with genetically modified *L. lactis* secreting the anti-inflammatory cytokine interleukin-10 (IL-10) provides localized delivery of a therapeutic agent through active *in situ* synthesis by this food-grade bacterium ([1]). The aim of this study was to further investigate the localization of *L. lactis* in normal versus inflamed intestinal tissue.
Methods : We prepared ileal loops in wild type (WT) and IL-10 deficient mice, which is a model of colitis. The loops were inoculated either with IL-10 producing *L. lactis*, control *L. lactis*, or sterile BM9 buffer. Samples for confocal laser scanning microscopy and transmission electron microscopy were collected after 30 minutes. For confocal laser scanning microscopy, cryosections of 20µ were incubated with a rabbit polyclonal antibody against *L. lactis*, followed by incubation with an Alexa488 anti-rabbit antibody and DAPI to visualize nuclei. Sections were examined with a Bio-Rad Radiance 2100 BLD system. Samples for electron microscopic analysis were processed according to the standard procedures for epon embedment and examined with a Zeiss TEM900.
Results : Confocal analysis showed a majority of bacteria in the lumen but some Lactococci could be detected *inside* the mucosal tissue of IL-10 deficient mice, which could be shown with series of optical sections of thick sections. Ultrastructural study showed *L. lactis* in inflamed epithelium, lamina propria and muscularis mucosae and in lacteals of IL-10 deficient mice but not of WT mice. WT mice showed no mucosal inflammation and bacteria were only observed in the lumen.
Conclusions : We may conclude from these observations that *L. lactis* can enter inflamed mucosal tissue and the lymphatic system. These results suggest that, rather than in the lumen, IL-10 production by *L. lactis* takes place after the bacteria have entered the nutrient-rich mucosa. The bacteria only enter inflamed mucosal tissue and do not pass healthy, normal epithelium.

1. L. Steidler, W. Hans, L. Schotte, S. Neirynck, F. Obermeier, W. Falk, W. Fiers and E. Remaut. Science 289 (2000), p. 1352-1355.

BILIARY-PANCREATIC AND LIVER DISEASES POSTERS

THE BASL REGISTRY OF NON ALCOHOLIC FATTY LIVER DISEASE (NAFLD). J. Henrion (1), S. De Maeght (2), M. Adler (3), S. Francque (4), P. Deltenre (5), C. de Galocsy (6), H. Orlent (7), W. Van Steenbergen (8), B. Bastens (9), E. Wain (10), P. Langlet (11), L. Lasser (11). (1) CH jolimont ; (2) CH Jolimont ; (3) Erasme, ULB ; (4) UZ, Antwerpen ; (5) CH Jolimont ; (6) HIS Bracops, Brussel ; (7) AZ St Jan, Brugge ; (8) Gasthuisberg, KUL ; (9) St Joseph, Liège ; (10) CH Verviers ; (11) Brugmann.

NAFLD is an emerging liver condition and is generally considered as the hepatic expression of the metabolic syndrome (MS). However, the demographic and metabolic characteristics of patients with NAFLD seen by hepatologists as well as the true prevalence of theMS and its components in these patients are not clearly established. Moreover the 'in the real life' attitude of Belgian hepatologists regarding the indication of a liver biopsy and the induction of a treatment is unknown. The aim of this registry was to answer these questions.
Methods : BASL members were invited to collect cases of NAFLD seen from Jan 1 to Dec 31, 2004 and to fill a questionnaire including demographic, clinical, biochemical, investigational and therapeutic data.
Results (preliminary) : 158 patients were collected until mid November 2004. Mean age and gender were 48.3 y and 87M/71F, respectively. Mean BMI WAS 30.9 (± 4.5) kg/m^2 and only 6 patients had normal BMI. The prevalence of the MS (according to NHANES, ATP III) was 53 % and the mean MS score (according to the presence of the 5 components) was 2.6 ± 1.2. Among the 5 components of the MS, excessive abdominal perimeter was observed in 77 %, fasting glycemia e110 mg/dl or treated diabetes in 40.6 %, elevated triglycerides (TG) e 150 mg/dl in 56.5 %, low HDL cholesterol in 41 % and arterial hypertension in 45.7 %. Only 3 patients had none of the MS features. Fasting insulinemia e20 µu/ml was observed in 54.7 % and was more elevated in patients with MS (mean 27.02 ± 10.9) than in patients without (mean17.65 ± 6.09, p = 0.0004). Marked increase in ALAT levels (> 5 × ULN) was observed in only 1.2 % of the cases, but marked increase of ggt (> 5 × ULN) was observed in around 10 % of patients (15/152). Patients with ggt > 5 × ULN were significantly older (55.9 v 47.64, p = 002), had more often treated diabetes (53 % v 22.6 %, p = 0.01)and had more elevated TG (median : 215mg v 159, p = 0.003). A liver biopsy was performed in 37.5 % and a pharmacological treatment was introduced by the hepatologist in 26 %. Large variations were observed between practitioners regarding their practical attitude.
Conclusions : 1) The typical NAFLD patient seen by hepatologists is a middle aged man or woman with slight obesity and hypertriglyceridemia. 2) NAFLD is linked to the MS, but only 53 % of the patients had this syndrome according to international definition. 3) Patients with marked elevation of ggt have peculiarities and it could be interesting to test if these patients have more severe liver fibrosis. 4) The attitude of practitioners regarding liver biopsy and treatment largely differs, reflecting the lack of evidences in these matters.

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A PILOT OBSERVATIONAL SURVEY OF HEPATITIS C IN BELGIUM. S. De Maeght (1), N. Bourgeois (2), C. de Galocsy (3), P. Langlet (4), P. Michielsen (5), H. Reynaert (6), G. Robaeys (7), D. Sprengers (8), M. Adler (9). (1) CH Jolimont ; (2) Hôpital Erasme ; (3) HIS Bracops ; (4) CHU Brugmann ; (5) UZ antwerpen ; (6) AZ VUB ; (7) Ziekenh. Oost-Limburg ; (8) CH St Augustinus, Antwerpen ; (9) Hôpital Erasme.

There is a lack of epidemiological data on hepatitis C (HCV) epidemics in Belgium. The aim of our study was to evaluate the feasibility of a national HCV observatory.
Methods :During one year (November 2003-November 2004), every new patient with HCV antibodies seen prospectively in 9 belgian centers by 17 hepatogastroenterologists was recorded and a standardized 10-item questionnaire was completed.
Results : Two hundred and sixty-five patients were recruited. ***Demographic and Clinico-biochemical characteristics*** were as follows : 55 % males ; median (IQR) age : 45 y (11-87) ; 86 % caucasians ; median (IQR) BMI and weight : 25 kg/m¸ (18-47)and 72 kg (46-137) ; risk factors for infection : IV drug use : 27 %, blood transfusion : 24 %, invasive medical procedures : 12 %, unknown : 22 %, other : 15 % ; year of first positive serology : < 1 : 46 %, 1-5 : 35 %, 6-10 : 12 %, 11-20 : 7 % ; discovery of HCV : fortuitous : 67 %, general symptoms : 27 %, extrahepatic signs : 5 %. Transaminases were normal in 34 %. Median elevation was 2 times normal value. On a QOL scale between 0-100, the mean was 61 ± 31 %. ***Virological data*** were as follows : RNA positive in 87 %, viral load above 800 000 IU/ml in 42 % ; genotype distribution : 1 : 60 %, 2 : 5 %, 3 : 19 %, 4 : 15 %, 5 : 2 %. ***Histological data*** showed : stage F0 : 12 %, F1 : 32 %, F2 : 34 %, F3 : 13 %, F4 : 9 % according to the Metavir classification. ***Antiviral treatment*** was proposed to 53 %. Reasons for non proposal included : normal ALT : 30 %, old age : 7 %, refusal : 3 % and others : 40 %.
Conclusions : This study highlights the feasibility of a national HCV survey using a simple questionnaire. This pilot study could be generalized throughout Belgium, allowing the follow up of the time-evolution of the epidemiological and medical characteristics of HCV.

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THREE MONTHS DATA FROM THE PEGINTRUST STUDY : PEGINTRON IN COMBINATION WITH REBETOL IN REAL LIFE IN BELGIUM. M. Adler (1), B. Bastens (2), I. Colle (3), J. Delwaide (4), J. Henrion (5), Y. Horsmans (6), P. Michielsen (7), J. Mulkay (8), F. Nevens (9), W. Van Steenbergen (9), P. Yap (11), H. Van Vlierberghe (10). (1) Hôpital Erasme, Brussels ; (2) Hôpital St Joseph, Liège ; (3) UZ Ghent, Ghent ; (4)CHU Liège, Liège ; (5) Hôpital Jolimont, La Louvière ; (6) UCL St Luc, Brussels ; (7) UZ Antwerpen, Antwerpen ; (8) CHU St Pierre, Brussels ; (9) KULeuven, Leuven (10) UZ Ghent, Ghent.

The applicability, in real life, of the results from large international randomised therapeutic trials in hepatitis C, is not well known. In an independent observational study, 64 clinicians from 46 different Belgian general and academic hospitals included, from January 2003 till October 2004, 241 patients with genotype 1, 4 and 5 and suffering from significant fibrosis, for treatment with PEG-IFNa2b and ribavirin during 12 months The population consists of 55 % male patients, the median age is 51 (IQR 22-78) ; median weight is 74 kg (IQR : 45-120) ; median BMI is 25 kg/ m^2 (IQR 17-42). Twenty three percent of the study group have an history of intravenous drug abuse ; 83, 14, and 3 % are patients with respectively genotype 1, 4 and 5 ; according to METAVIR 58, 22 and 20 % show respectively stage 2, 3 and 4 fibrosis and baseline viral load is above 800,000 IU/ml in 49 % of the patient population. Therapy had to be discontinued before the planned term and within the first 3 months of treatment in 21 patients (8.7 %). Reasons for withdrawal are non-compliance in 4 patients, adverse events in 11 and serious adverse events in 6 subjects. The median time lag between starting and stopping treatment is 73 days (IQR 18-99). One patient died from septic shock and multiple organ failure. Early virological response (EVR) is 67 % i.e. observed in 95 patients out of 141, for whom all virological data are available at month 3. From these preliminary data, we can conclude that, compared to the Mann's trial ([1]) and the Davis' analysis ([2]), Belgian patients treated in real life are leaner, older, suffer from more advanced fibrosis while achieving similar EVR and lower early treatment discontinuation rate.

1 Lancet 2001 ; 2 Hepatology 2003

VALUE OF THE FIBROTEST FOR THE STAGING OF HEPATITIS C : AN EXTERNAL VALIDATION STUDY.
M. Adler (1), P. Thiry (1), B. Frotscher (1), S. Evrard (1), T. Gustot (1), N. Nagy (1), P. Langlet (2), N. Bourgeois (1).
(1) Hôpital Erasme, Brussels ; (2) CHU Brugmann.

There is an urgent need of reliable non-invasive markers of liver fibrosis, as an alternative to liver biopsy which has disadvantages and drawbacks. The Fibrotest (FT) is one of them but has been validated externally only in one study with lower predictive values ([1]). Of the 133 FT values performed in our unit since June 2004, 17 (13 %) were outside the 99 percentiles : 4 with haptoglobin < 5 mg/dl, 4 with haptoglobin > 320 mg/dl, 3 with apo A1 > 250 mg/dl, 1 with apo A1 < 73 mg/dl and 5 with a2 macroglobulin < 110 mg/dl. The FT was done in parallel with liver biopsy with a fibrosis staging according to METAVIR (MV) classification in 33 HCV patients. When the FT fibrosis stage estimate was ? 2 (i.e. 0.49-1), this was confirmed by MV in 14 of the 15 patients (93 %). When it was between 1 and 2, this was confirmed in 6 of the 6 patients (100 %). When it was < 2 (11 patients), MV was 0 or 1 in 6 but 5 patients (45 %) had discordant results : 4 MV2 and 1 MV3. FT area under the ROC curves for significant (F0-F1 vs F2-F4) and severe (F0-F1-F2 vs F3-F4) fibrosis was 0.80 and 0.88 respectively.
Conclusion : our external validation study confirm the excellent specificity of FT as a simple non-invasive quantitative estimate of significant liver fibrosis but it was inadequate to predict absence or minimal fibrosis.

1. Rossi *et al*., Clin Chem 2003.

LIVER FAILURE REQUIRING LIVER TRANSPLANTATION (LTX) FOLLOWING WEIGHT-REDUCTION SURGERY FOR MORBID OBESITY.
A. Risha, B. Van Gheluwe, V. Donckier, J. Lerut, R. Troisi, O. Detry, D. Ysebaert, R. Aerts, J. Fevery, F. Nevens, J. Pirenne. University Hospitals Leuven and Belgian Liver Transplant Centers.

Due to increased incidence of obesity, obesity-induced liver failure, particularly Non-Alcoholic Steato-Hepatitis (NASH) has become an increasing indication to LTx. It is usually accepted that weight-reduction is an effective therapy for obesity-induced liver failure. This reasoning was recently questioned by patients at our center who presented with liver failure requiring LTx after weight-reduction surgery. To determine whether this observation was casuistic or corresponded to a real biological event, (i) these 3 cases were reviewed ; (ii) a literature research on the influence of weight-reduction on liver function was conducted ; and (iii) a Belgian survey was conducted.
Results : (i) 3 morbidly obese patients who underwent Intestinal Bypass (IBP) were diagnosed with (sub)acute (n : 2) and chronic (NASH/n :1) liver failure following IBP and received LTx. Graft and patient survival is 100 % (follow-up : 5-to-20 months). In 2 of 3 patients, intestinal continuity was restored during LTx but this led to NASH in 1 and relapsing morbid obesity in another. (ii) A meta/analysis (517 studies, *Am J Med 2003*) found no evidence to support (or refute) the protective effect of weight-reduction against NASH. A Pubmed research shows that potentially fatal liver failure has been seen after bariatric surgery (mostly IBP). The risk is inferior when gastroplasty alone is done, although gastroplasty increases the degree of hepatitis in some patients. (iii) A Belgian survey indicates that acute and chronic liver failure requiring LTx has been encountered after weight-reduction surgery (mostly IBP) in at least 7 additional patients.
Conclusion : Weight-reduction does not *necessarily* protect from NASH. In particular, IBP perhaps by causing a rapid weight loss (fatty-acids mobilization) and/or a ‘short-bowel-like’ syndrome may trigger NASH. In addition, weight-reduction surgery may increase susceptibility to idiosyncratic acute liver failure. Enhanced hepatological surveillance and elimination of potentially hepatotoxic drugs is warranted in all patients undergoing medical/surgical weight-reduction.

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EUROPEAN NETWORK FOR VASCULAR LIVER DISORDERS "EN-VIE" : PROSPECTIVE DATA DURING THE FIRST YEAR. P. Langlet (1), L. Lasser (2), J. Martinet (3), P. Gruselle (4), M. Adler (5), S. Murad Darwish (6), H. Janssen (6), J. Delwaide, J. Garcia-Pagan (8), E. Elias (9), M. Primignani (10), D. Valla (11). (1) CHIREC and CHU Brugmann, ULB ; (2) CHU Brugmann, VUB-ULB ; (3) Clinique Mont-Godinne, UCL ; (4) CHU Vésale, ULB ; (5) Hôpital Erasme, ULB ; (6) Erasmus Hospital, Rotterdam, NL, CHU Sart Tilman ; (8) Hospital Clinic I Provincial de Barcelona,SP ; (9) Queen Elisabeth Hospital, Birmingham,UK ; (10) IRCSS Ospedale Maggiore di Milano, Ita ; (11) Hôpital Beaujon, Paris, France.

Introduction : Vascular diseases of the liver represent a heterogeneous group of rare disorders usually affecting young subjects and associated with a poor spontaneous outcome. Hepatic vein thrombosis "Budd-chiari syndrome" (BCS) and non tumoral and non cirrhoric acute portal vein thrombosis (PVT) remain under-recognized and poorly understood disorders. Treatments of these disorders (anticoagulation, surgery,...) have been empirically developped and poorly assessed. Because limitations associated with retrospective studies, we started1october 2003, a prospective European study(with European Comunityfunding) to collectall cases of BCS and PVT during at least 2 years in 10 european countries.
Aims : To collect high quality data for clinical studies in a large cohort of patients investigated and managed in the most appropriate possible manner. To merge these data into a large European data base to analyses on cause, prognosis and assessement of therapy. To collect and register well characterised samples for clinical and basic investigations in national level and in Europe.
Methods : Since 1 october 2003, all > 16 years old patients with newly diagnosed BCS or PVTwithout tumoral causehad to be notified to EN-Vie investigator in a national level. After informed consent, registration was performed and baseline and follow-up data were completed in an European electronic Case report form. Results from available European and Belgium data are shown below. More complete data will be presented in february.
Results : 147 patients (74BCS and 73 PVT)are registered in the study in1 year with81 % BCS and 84 % PVT eligible. In Belgium, 5 BCS (national level) and 3 acute PVT (only in the investigator center) were included. For BCS : median age = 45.9 years with 76 % female. Duration of disease before diagnosis was < 1 month in 42 % ; 1-6 month in 42 %and > 6 months in 16 %. The majority of patients had Child-Pugh B (62 %) whereas 23 % had Child-Pugh C. In 16/25 pts hypercoagulable aetiology was found. For PVT : median age = 43,5 years with 56 % female. Duration of disease before diagnosis was < 1 month in 83 %. Hypercoagulable aetiology was found in 50 % of cases. The majority of patients had no liver insuffisiency (Child-Pugh A = 62 %) and anticoagulation was given in 66 % of PVT.
Conclusions : Vascular liver disorders are very rare. Prospective studies are required to collect a large number of patients followed-up for a long period of time. Underlying causal factors are likely to have a great impact on the outcome. Adjustement on prognostic variables in a large cohort will be neccessary.

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WARREN SHUNT (WS) FOR PORTAL HYPERTENSION (PHT) DUE TO IDIOPATHIC PORTAL VEIN THROMBOSIS : BACK TO SHUNT-SURGERY ? J. Pirenne, V. Janssens, D. Monbaliu, F. Nevens, J. Fevery, I. Hoffman. University Hospitals Leuven.

With the development of Transjugular Intrahepatic Portosystemic Shunt (TIPS) and Liver Transplantation (LTx), indications to shunt-surgery for Portal Hypertension (PHT) have virtually vanished. An exception is when the portal vein is thrombosed rendering TIPS anatomically impossible. We report 5 patients {3males/2females ; 17.5yo (8.1-33)} with isolated portal vein thrombosis and major PHT {bleeding (n : 4), splenomegaly/hypersplenism (n : 5)} refractory to beta-blocker (n : 3) & sclerotherapy (n : 4). They had preserved liver function and thereby were not candidates for LTx. A selective distal spleno-renal Warren Shunt (WS) was performed in all. A 6th patient (15.6 yo female) with non-cirrhotic PHT (and an open portal vein) was also treated with a WS. In short, the splenic vein proximal to the superior mesenteric vein was dissected-free from the inferior edge of the pancreas, transsected and widely anastomosed end-to-side to the anterior aspect of the left renal vein. This was immediately followed by a substantial venous pressure drop in the splenic sector. There was no need for transfusion during surgery and there was no procedure-related morbidity/mortality. Postoperative course was uneventful and PHT improved/disappeared in all 6 patients. No case of esophagal bleeding was encountered since then. Selectivity of this shunt is supported by absence of encephalopathy and preservation of liver function. All patients -except 1 with a complex immunodeficiency/bronchiectasia syndrome- are now enjoying a normal life-style including sport activities which were prohibited before surgery due to massive splenomegaly, low platelets count and risk of splenic rupture. Shunt patency (Echo) is 100 %. Follow-up is 52-to-2 months.
In conclusion, the distal spleno-renal WS is efficient in patients with isolated portal vein thrombosis and refractory PHT. In view of the efficacy, low morbidity and selectivity of this shunt, it is tempting to (re)consider its use as an alternative to TIPS (even in presence of an open portal vein), in stable patients with preserved liver function and who are not directly LTx candidates.

- D66 -

CONTRIBUTION OF MAGNETIC RESONANCE FOR THE ASSESSMENT OF PORTAL HYPERTENSION : CORRELATIONS WITH DOPPLER ULTRASONOGRAPHY AND HEPATIC VENOUS PRESSURE GRADIENT.
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The contribution of magnetic resonance imaging (MRI) as a non-invasive procedure to assess portal hypertension in cirrhotic patients is still not determined.
Aims of the study : To prospectively evaluate the technical feasibility and the reproducibility of portal hemodynamic measurement by contrast-enhanced MRI using the following parameters : portal blood flow and diameter, azygos blood flow. These measurements were correlated to US Doppler and invasive findings (HVPG).
Methods : 17 consecutive cirrhotic patients with no previous bleeding and at least grade 2 oesophageal varices underwent at 8 weeks interval (T0 and T8) - by the same operator each time- hepatic MRI, Doppler Ultrasonography and HVPG measurement.
Results : Measurements by MRI of portal venous blood flow and diameter were obtained for all the patients. Azygos blood flow quantification failed in 5 of 17 patients. A significant correlation was observed between the values of portal blood flow and portal diameter obtained for each patients at T0 and T8 ($p = 0.0001$ and 0.0001, respectively). No correlation was observed between HVPG and MRI data, except a negative correlation between HVPG and portal vein diameter, at T0 and T8. No correlation was found between HVPG and portal blood flow, velocity and diameter assessed by Doppler Ultrasonography. *Results are expressed in median and range.*

MRI	**n**	**T0**	**T8**	**Spearman (NP correlation)**
Portal blood flow (ml/min)	17	743 (80-2340)	676 (133-1295)	p = .0001
Portal diameter (mm)	17	12 (8-19)	12 (8-16)	p = .0001
Azygos blood flow (ml/min)	12	258 (115-432)	158 (45-290)	NS

Conclusions : MRI is reproducible and can be helpful for the assessment of portal hypertension. However, correlations with Doppler US and HVPG are weak in a homogenous group of patients who had never bled from their varices and its use in clinical practice remains to be assessed in this particular setting.

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LONG-TERM RESULTS OF MULTIVISCERAL SPLANCHNIC TRANSPLANTATION.
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Multivisceral splanchnic transplantation (MVTx) {defined as Tx of the liver, pancreas, and various segments of bowel} is usually seen as a high-risk surgical procedure with substantial perioperative morbidity/mortality and is not frequently performed. In an era of profound liver shortage and increasing mortality (~20 %) on LTx alone waiting list, it is questionable whether MVTx should be performed at all. This is particularly important since Eurotransplant (*organ allocation organism*) currently gives priority to MVTx *versus* LTx alone recipients. The purpose of this study was therefore to reevaluate the long-term results of MVTx. Of 280 LTx done at our center since 2000, 4 (1.5 %) were MVTx. 2 MVTx included the liver, the entire duodenum, and the pancreas. This was in patients with combined type I diabetes and irreversible liver disease (primary sclerosing cholangitis in a 21yo female and subacute liver failure-NASH in a 46yo male). 2 other MVTx included the liver, the entire duodenum, the pancreatic head, and the entire jejuno-ileum. These were 2 females aged 56yo and 57yo and suffering from short-bowel syndrome (due to bowel ischemia) *plus* TPN-induced liver failure. The basic design of the operation was identical in all 4 patients : In short, the MVTx splanchnic graft (liver *in continuity* with the duodeno-pancreas, and the jejuno-ileum in the last 2 patients) was procured and transplanted *en bloc* with an aortic conduit including both the celiac trunk and the superior mesenteric artery. Supra- and infra-hepatic vena cava were reimplanted in a way similar to conventional LTx, and under veno-venous by-pass. Aortic anastomosis was end-to-side onto the recipient aorta. Native portal vein was anastomosed piggy back onto the grafted portal vein. Biliary drainage was through a duodeno- (or jejuno-) jejunostomy. Operations were uneventful. Hospital stay was 2 and 4 weeks and complication-free in the first 2 patients. It was longer in the last 2 patients in whom the intestine was included in the MVTx graft (up-to-3 months). This was due to the need for more intense medical and immune surveillance posttransplant when the entire small bowel is transplanted. All 4 patients are liver disease-free, insulin-free, TPN-free and are eating normally at last follow-up (1.5-to-4.5 years). All 4 patients are physically and socially fully rehabilitated and are following a normal life-pattern. A rejection episode was seen following non-compliance in one patient but responded promptly to reestablishment of immunosuppression.
In conclusion, MVTx has evolved into a well-standardized and safe surgical procedure. It provides excellent survival in selected critically-ill patients suffering from complex multi-organ disease/failure and who would otherwise rapidly succumb. Prioritizing the allocation of livers to prospective MVTx candidates seems therefore justified.

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TUMOR VASCULAR TARGETING THERAPY IN RODENT MODELS OF LIVER METASTASES : NONINVASIVE MONITORING WITH ADVANCED MRI. F. Chen (1), X. Sun (1), F. De Keyzer (1), J. Yu (1), V. Vandecaveye (1), W. Landuyt (2), H. Bosmans (1), R. Hermans (1), G. Marchal (1), Y. Ni (1). (1) Herestraat 49, Department of Radiology, UZ, Leuven ; (2) Herestraat 49, Laboratory of Experimental Radiobiology / LEO, UZ, Leuven.

Purpose : To monitor the treatment of liver tumors in rats with a vascular targeting agent Combretastatin A-4-phosphate (CA-4-P) using comprehensive magnetic resonance imaging (MRI) in correlation with microangiographic and histopathologic findings.
Materials and methods : Thirty rhabdomyosarcomas (R1) of 8-14 mm in diameter were ready 16 days after implantation in the right and left liver lobes of 15 rats. All rats were examined with a 1.5T MR scanner and a 4-channel wrist coil. T2-weighted MRI (T2WI), pre- and post-contrast T1-weighted MRI (T1WI), diffusion-weighted imaging (DWI), and dynamic susceptibility contrast-enhanced MRI (DSC-MRI) with relative blood volume (rBV) and flow (rBF) maps were acquired at baseline, 1 and 6 h till 2 days after intravenous injection of CA-4-P at 10 mg/kg (9 dosed rats and 6 controls). In vivo data including tumor volume, signal intensity (SI), apparent diffusion coefficient (ADC), rBV and rBF were correlated with ex vivo microangiography and histopathology.
Results : CA-4-P treated tumors grew significantly slower than that of controls ($p < 0.01$). Vascular shutdown was evident at 1h but overwhelming at 6h on post-contrast T1WI. Enhanced rim indicative of neovasculature occurred at the periphery 2 days after treatment. The tumor ADC decreased gradually till 6 h but increased at two days especially in the central region ($P < 0.01$). Both ADC map and high b-value DWI enabled distinction between necrotic and viable tumors. Tumor rBV and rBF decreased sharply at 1 to 6 h, and partially recovered at 2 days. Tumor SI-time curve reflects well the therapeutic response as verified by postmortem microangiographic and histologic findings.
Conclusion : The present clinical MRI unit allowed vivid monitoring of CA-4-P related dramatic vascular shutdown, necrosis and angiogenesis of liver tumors in rats. Single dose of CA-4-P is insufficient for tumor eradication and combined therapeutic regimes are warranted. The experimental setting demonstrated in this study may prove useful for both laboratory research and clinical applications.

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HEPATIC RADIOFREQUENCY COAGULATION : PERCUTANEOUS OR SURGICAL APPROACH? A MULTIVARIATE META-ANALYSIS. S. Mulier (1), Y. Ni (2), J. Jamart (1), T. Ruers (2), G. Marchal (3), L. Michel (1). (1) UCL Mont-Godinne ; (2) UMC Nijmegen, Nl ; (3) KULeuven.

Objective : The purpose of this study was to analyse the factors that influence local recurrence after radiofrequency coagulation of liver tumors. Summary Background Data : Local recurrence rate varies widely between 2 and 60 %. Apart from tumor size as an important risk factor for local recurrence, little is known about the impact of other factors.
Methods : An exhaustive literature search was carried out for the period from January 1st 1990 to January 1st 2004. Only series with a minimal follow-up of 6 months and/or or mean follow-up of 12 months were included. Uni- and multivariate meta-analyses were carried out. Results : Ninety-five independent series were included, allowing the analysis of the local recurrence rate of 5,224 treated liver tumors. In a univariate analysis, tumor-dependent factors with significantly less local recurrences were : smaller size, neuroendocrine metastases, non-subcapsular location and location away from large vessels. Physician-dependent favorable factors were : surgical (open or laparoscopic) approach, vascular occlusion, general anesthesia, a 1 cm intentional margin and a greater physician experience. In a multivariate analysis, significantly less local recurrences were observed for small size ($p < 0.001$) and a surgical (versus percutaneous) approach ($p < 0.001$).
Conclusions : Radiofrequency coagulation by laparoscopy or laparotomy results in superior local control, independent of tumor size. The percutaneous route should mainly be reserved for patients who cannot tolerate a laparoscopy or laparotomy. The short-term benefits of less invasiveness for the percutaneous route do not outweigh the longer-term higher risk of local recurrence.
Table : **Local recurrence rate according to size and approach.**

	Percutaneous	**Laparoscopy/laparotomy**
£ 3 cm	16.0 %	.6 %
3 - 5 cm	25.9 %	21.7 %
> 5 cm	60.0%	50.0%

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PERCUTANEOUS AND SURGICAL RADIOFREQUENCY ABLATION FOR LIVER MALIGNANCIES : A DIFFERENT PHILOSOPHY OF TREATMENT ? C. Hubert (1), J. Gras (1), P. Goffette (2), Jm. Grajeda (1), B. Van Beers (2), L. Annet (2), Y. Horsmans (3), C. Sempoux (4), J. Rahier (4), F. Zech (5), J-F. Gigot (1). (1) Hepatobilio-pancreatic Unit ; (2) Radiology ; (3)Gastroenterology ; (4) Pathology ; (5) Internal Medicine, Saint-Luc University Hospital, UCL, Brussels.

Purpose : to report a single institutional experience with radiofrequency ablation (RFA) techniques for primary and secondary liver malignancies.
Patients and methods : Sixty-five patients underwent RFA technique through a percutaneous (Group I : 33 patients) or a surgical approach (Group II : 32 patients). The two groups are different according to type of disease selection (more hepatocellular carcinoma in Group I and liver metastases in Group II) and tumour features (smaller size but greater number of lesions in Group II). The RFA technique was more radical in Group II, with a greater number and a longer duration of RFA applications. In Group II, liver resection was associated in 23 patients (72 %) (including 5 patients with RFA assisted wedge liver resections), in order to increase resectability.
Results : The 60-days postoperative mortality and complication rates were low and not significantly different in both groups. The postoperative hospital stay was longer in Group II. During a median follow-up of 24 months in Group I and 21 months in Group II, the “in-situ” recurrence rate was 41.4 % and 9.1 %, respectively ($p < 0.001$). Multivariate statistical analysis demonstrated that tumour size > 2cm and type of approach for RFA technique (percutaneous versus surgical) were independent predictive factors of “in-situ” liver tumour recurrence.
Conclusions : RFA is a safe technique for treating liver malignancies. Results differences in both approaches are explained by differences in treatment philosophy, technical conditions and tumour size selection. Despite these features, open surgical approach appears to be more efficient without increasing treatment mortality and morbidity.

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LATE SURVIVAL AFTER SURGICAL RESECTION OF PRIMARY LIVER MALIGNANCIES IS LINKED TO UNDERLYING CHRONIC LIVER DISEASE. C. Hubert (1), C. Sempoux (2), J. Rahier (2), Y. Horsmans (3), A. Geubel (3), B. Van Beers (4), L. Annet (4), F. Zech (5), D. Leonard (1), Jf. Gigot (1). (1)Hepatobiliopancreatic Unit, (2) Pathology, (3) Gastro-Enterology, (4) Radiology (5) Internal Medicine, Saint-Luc University Hospital, UCL, Brussels.

Background : to report a single institutional experience with surgical resection of primary liver malignancies.
Patients and methods : 65 patients suffering from HCC (Group I : n = 55) and CCC (Group II : n = 10) underwent surgical resection. Group I was subdivided in HCC on normal liver (Group I-A : n = 29) and HCC on chronic liver disease (CLD) (Group I-B : n = 26). Patient’s clinical data and tumour features were not different in all groups, except for median patient’s age and ASA status which were significantly greater in group I-B. Radical liver resection was obtained in 96 %) and 90 % of HCC and CCC. Four HCC patients underwent associated radiofrequency thermoabla-tion for contralateral or multiple lesions. Types of liver resections included major hepatectomies in 45 % and 70 % of HCC and CCC (NS).
Results : 60-days mortality was 0 % in Group I-A and Group II and 4 % in Group I-B (NS). The 5-year overall (OS) and disease-free survival (DFS) rates were respectively 54.9 % and 35 % in HCC and 60 % and 49 % in CCC patients (NS). However, the 5-year OS and DFS were 71 % and 59 % in Group I-A and 37 % and 6 % in Group I-B. Multivariate statistical analysis demonstrated in HCC patients that chronic liver disease, poor differentiation, satellites nodules and male sex were significant adverse predictive factors of survival.
Conclusions : Surgical resection for primary liver cancers is safe and effective with attractive OS and DFS, except when associated with underlying CLD which is the worst prognostic factor of bad outcome.

ENDEMY OF ALVEOLAR ECHINOCOCCOSIS IN SOUTHERN BELGIUM ? C. Honoré (1), O. Detry (1), O. Wauters (1), J. Delwaide (2), J. Demonty (3), A. Thiry (4), A. Deroover (1), M. Meurisse (1), J. Belaïche (4), P. Honoré (1). (1) Dpt of Abdominal Surgery and Transplantation ; (2) Dpt of Hepatogastroenterology ; (3) Dpt of infectious diseases and Internal Medicine ; (4) Dpt of Pathology, University of Liège, CHU Sart Tilman B35, B-4000 Liège.

Introduction : Belgium is not considered as a country at risk for alveolar echinococcosis. However, it was recently demonstrated by necropsy that, in some regions of southern Belgium, 20 % to 50 % of the red foxes are infected by E. Multilocaris. The aim of this paper is to report the experience of a single institution with management of alveolar echinococcosis contracted in southern Belgium.

Patients and Methods : Cases of autochthonous alveolar echinococcosis were prospectively included. In a 3-year period, 4 patients (mean age : 70 years) were diagnosed with alveolar echinococcosis and underwent extensive evaluation and treatment. None of them had recent journeys in country at risk for E. Multilocaris. Results : Two cases presented as a hepatic mass from unknown origin. After extensive evaluation they underwent R0 liver resection and pathology revealed alveolar echinococcosis. They received albendazole adjuvant therapy and are alive and well at follow-up. Two other patients presented with large liver mass that were observed for a variable period of time before being sent to the author's institution. Echinococcosus serum tests became positive at that time and alveolar echinococcosis diagnosis was made. Due to pulmonary lesions curative surgical resection was not possible and they were palliatively treated with albendazole.

Conclusion : Alveolar echinococcosis should be considered as possible diagnosis when a hepatic mass from unknown origin is evaluated, especially in southern Belgium. Early diagnosis may allow curative resection. These 4 cases show that we are maybe at the eve of an endemic alveolar echinococcosis in Belgium.

PANCREATITIS-INDUCED ARTERIAL COMPLICATIONS : RESULTS OF TRANSCATHETER EMBOLIZATION. G. Maleux (1), V. Goosens (1), S. Heye (1), G. Wilms (1), W. Van Steenbergen (2). (1) Radiology, (2) Hepatology, University Hospitals, Leuven.

Purpose : In a retrospective study, we evaluated the efficacy, safety, and long-term clinical outcome of pancreatitis-induced arterial complications managed by transcatheter embolotherapy.

Materials and methods : Between August 1992 and October 2004, 15 consecutive patients (12 men, 3 women) with a mean age of 53.8 yrs (range 38-69 yrs) underwent transcatheter embolization of a pancreatitis-related arterial complication. In 8 patients, the underlying disease was chronic pancreatitis, the remaining 7 patients suffered from acute pancreatitis. Pancreatitis was caused by alcohol abuse (n = 10), biliary stones (n = 2), post-ercp (n = 1), and was of unknown origin in one case. Indications for angiographic evaluation and subsequent transcatheter embolization were epigastric pain (n = 5), gastrointestinal haemorrhage (n = 3), retroperitoneal haemorrhage (n = 3), external haemorrhage via abdominal drain (n = 1), and asymptomatic CT-findings (n = 4).

Results : Selective visceral angiography revealed a pseudoaneurysm (n = 12), a pseudoaneurysm with clear contrast extravasation (n = 3), and an arteriovenous fistula (n = 1). Injured arteries were the gastroduodenal artery (n = 3), pancreaticoduodenal arcade (n = 5), middle colic artery (n = 1), splenic artery (n = 5), right hepatic artery (n = 1), and the left gastric artery (n = 1). Embolization was performed with different embolic agents : vascular coils (n = 10), microparticles (n = 2), glue (n = 1), glue and coils (n = 1), and microparticles, glue and coils (n = 1). One embolization session was performed in 12 patients ; the remaining 3 patients needed a second embolization within one week after the first session. In three patients intentional occlusion of the splenic artery resulted in partial splenic infarction. Clinical follow-up (mean period 56 months ; range 1-141 months) revealed no late recurrence of symptoms. Four patients (27 %) died during follow-up due to multiple organ failure (n = 1), acute pancreatitis (n = 1), suicide (n = 1), and cerebral haemorrhage (n = 1).

Conclusion : Transcatheter embolotherapy is a minimally-invasive but very effective and durable treatment modality to definitively manage arterial complications related to pancreatitis. Partial splenic infarction can occur and is directly related to the intentional coil-occlusion of the splenic artery. Twenty-seven percent of the patients died during further follow-up, not of bleeding but of a non-related condition.

DUODENUM PRESERVING CEPHALIC OR SUBTOTAL PANCREATECTOMY : RESULTS OF A LESS INVASIVE SURGICAL CONCEPT. A. Dili, C. Bertrand, B. Mansvelt, G. Molle, N. Tinton. CH Jolimont-Lobbes.

In 1980's, Beger *et al.*, considering the head of the pancreas as the pacemaker of chronic pancretitis, reported DPRHP as a less mutilating operation than the Whipple procedure. In order to preserve endocrin and exocrin pancreatic function, Frey developped a similar procedure. DPRHP has recently been performed for pancreatic pathologies other than CP.We review our experience of these surgical procedures.

Methods : From June 1992 to October 2004, 18 DPRHP were performed in our institution. Population : 18 p (13 men, 5 women), aged from 3 months to 67 years old. Asa I (2p), II (10p), III (5p), IV (1p).

Indications : 4 tumors (1 muc. cystadenoma of the head, 2 adenoc. of the isthmus and the corpus, 1 nesidioblastosis), 1 trauma of the isthmus, 13 CP. All CP patients suffered from chronic pain (11 consumed morphine) and were hospitalised regularly (preop admission 1-15). CP were complicated with 8 biliary stenosis, 4 duodenal stenosis, 2 HTP, 10 pseudocysts, 4 splenic complications, 2 hemorrages. Technics : 8 Beger, 7 Frey, 3 subtotal pancreatect.

Results : Operating time : 270-570 min (m 403.3), no peroperative complications.Postoperative morbidity : 66.6 % : no pancreatitis,no biliary fistula, 5 pancreatic fistulas with no clinical signification, 1 duodenal perforation necessitating a Whipple procedure (5.5 %), 3 gastric stasis (16.6 %), 1 abces (5.5 %), 1 biliary stenosis (5.5 %) 1 hemorrage (5.5 %). Reoperation rate : 5.5 % (1 for duodenal perforation). Postoperative mortality : 1p died from ARDS and intraabdominal hemorrage (5.5 %). Hospital stay :9-46d (m 21.5d). Late postoperative course (from 2 to 138 months) : de novo diabete : 4p (22.2 %), de novo exocrin pancreatic insufficiency : 3p (16.6 %), 2 incisional hernias(11.1 %), 1 occlusion with peritonitis. Considering pain among 13 CP patients, only one, who relapses alcohol abuse and has caudal pseudocysts, still suffers invalidant pain and needs morphin ; 1p has occasional pain due to mesenteric angor. From 4 tumor suffering patients, 1p needs morphin for tumor reccurence, 2p died from non pancreatic related diseases.

Conclusion : DPRHP is a «tissu-saving» procedure that can be performed for various pancreatic pathologies. In chronic pancreatitis, these techniques controlled all the disease's related complications in all patients, excepted, after several years, in one patient (with relapsing huge alchohol abuse and caudal pancreatic pseudokyst).

Invited lecture

- L 01 -

NEW INSIGHTS INTO THE CELLULAR IMMUNOLOGY OF THE INTESTINE. D. Latinne. Cliniques Universitaires St Luc, Bruxelles.

The classical theory of T helper cell activation pathways and cytokine involvement in pathogenesis of inflammatory bowel disease (IBD) is Th1 in Crohn's disease (CD) and partial Th2 in ulcerative colitis (UC). This view seems now to simplistic and imunological models are proposed that involve both clusters of cytokines.
Crohn's disease (CD) is thought to result from the association of environmental and genetic factors to an upregulated aggressive immune response and chronic inflammation. Recently, it has been suggested that CD doesn't only result from dysregulated adaptive response but that innate immune response might play a role in the inductive phase : epithelial barrier defect, production of inflammatory cytokines (IL1, TNFa, IL6, IL12…) and defective neutrophil function in response to mucosal bacteria trigger a T helper adaptive immune response. Both Th1 and Th2 cytokines (IL2, IFNg, IL4, IL13…) seem to play a role in the effector phase. However, activation of T helper cells can only lead to effective immune response if co-stimulatory molecules expressed on activated T cells (CD40L, ICOS, CD28…) bind to their specific ligands on the antigen presenting cells (macrophages, dendritic cells…), mesenchymal or endothelial cells (CD40, B7h, CD80/86…). This binding is necessary to generate an effective immune response, to enhance production of chemokines, expression of adhesion molecules and T cell recruitment promoting chronic inflammation. Their expression has been shown to be increased in IBD.
This T cell immune response is normally controlled by regulatory T cells (Tr). A defective function of this population might contribute to excessive T cell response and chronic inflammation. CD4+CD25+ regulatory T cells in healthy individuals are derived in the thymus and represent 5-10 % of T cells in peripheral lymphoid organs. They down-regulate the immune response through IL10 and TGFb production. In IBD, it has been suggested that effector T cells might negatively regulate the development of Tr cells in the thymus. This can be associated to another defective mechanism reported in CD : a T cell resistance to apoptosis leading to inappropriate immune homeostasis and accumulation of T cells in the tissues.
A better understanding of the interaction between all these factors might contribute to the adequate use of the newly emerging therapeutic agents.

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- L 02 -

FUNCTIONAL STUDY OF CARD15 AND TOLL-LIKE RECEPTOR 4 POLYMORPHISMS IN MONOCYTES OF CROHN'S DISEASE PATIENTS. H. Peeters (1), S. Bogaert (1), D.Laukens (2), D. Elewaut (2), P. Rottiers (3), F. De Keyser (2), M. De Vos. (1) Departments of Gastroenterology and (2)Rheumatology, (3) Ghent University Hospital and Department of Molecular Biomedical Research, Ghent University – VIB, Gent, Belgium.

Objectives : CARD15 and Toll-like receptor 4 (TLR4) are respectively intracellular and membrane-bound receptors for bacterial cell wall components (respectively muramyldipeptide (MDP) and lipopolysaccharide (LPS)). Polymorphisms in the genes of CARD15 (snp8, snp12 and snp13) and TLR4 (Asp299Gly) have been linked with Crohn's disease (CD). However, the exact effect of these polymorphisms is still not fully understood. Existing data mostly arose from in vitro studies on transfected cell lines. A few ex vivo studies have been performed, however with a limited number of patients. Therefore, we wanted to investigate ex vivo the functional impact of these polymorphisms on isolated monocytes (Mo) from CD patients.
Methods : 47 CD patients were included in this study. CARD15 and TLR4 genotypes were determined using RFLP-PCR. Mo were isolated from peripheral blood mononuclear cells using magnetic cell sorting (MACS), cultured and stimulated (2 or 8 h) with LPS 10ng/ml, MDP 100 ng/ml and adhero-invasive E. Coli (AIEC, a strain predominantly found in CD patients) 10^7/ml. Cytokine production (IL1?, IL6, IL8, IL10, IL12p70, TNF) was assessed by RT-PCR (2h), Cytometric Bead Array (CBA) (8h) and ELISA (8h). Results were linked with the presence of polymorphisms.
Results : In patients with CARD15 polymorphisms, Mo stimulated with AIEC for 8 h, produced significantly less IL1? (mean 24139 vs 34097 pg/ml, $P < 0.05$) and IL10 (mean 302 vs 551 pg/ml, $P < 0.05$) and less IL6 (mean 21944 vs 29804 pg/ml, $p = 0.07$) and IL8 (mean 45729 vs 55372 pg/ml, $p = 0.25$) compared to wildtypes. There were no differences in unstimulated Mo or after stimulation with MDP. The response to AIEC was not different between single heterozygotes and compound heterozygotes or homozygotes, nor between the different CARD15 polymorphisms (snp8, 12 or 13). TLR4 polymorphisms did not influence Mo response after LPS and AIEC stimulation.
Discussion : Monocytes of CD patients carrying CARD15 polymorphisms show a disturbed inflammatory response after stimulation with adhero-invasive E. Coli. For the first time a functional problem was detected in single heterozygous carriers of CARD15 variants. Further functional studies are currently ongoing. Heterozygous carriage of TLR4 polymorphisms has no influence on Mo function.

- L 03 -

PROFILE OF SOLUBLE CYTOKINE-RECEPTORS IN CROHN'S DISEASE : SERUM SOLUBLE INTERLEUKIN (IL)-1 RECEPTOR TYPE II (SIL-1RII) IS A MARKER OF DISEASE ACTIVITY. T. Gustot (1), A. Bitton (2), E. Louis (3), G. Frottin (2), C. Collette (2), M. Edwards (2), A. Cohen (2), J. Belaiche (3), G. Wild (2), A. Van Gossum (1), J. Devière (1), D. Franchimont (2). (1) Erasme Hospital, Brussels, Belgium ; (2) McGill Health center, Montréal, Canada ; (3) CHU Liège, Sart-Tilman, Belgium.

Background and Aims : Crohn's disease (CD) is a chronic relapsing auto-inflammatory disease. Many auto-inflammatory syndromes are related to a dysregulated signaling of IL-1b. Interleukin-1b (IL-1b) is a key factor in the pathogenesis and course of CD. Soluble IL1RII is a cytokine scavenger of IL-1b and a major inhibitor of IL-1b signaling. We sought to examine serum sIL-1RII levels in CD and in a prospectively followed CD patient population.
Patients and Methods : ***Test cohort*** : We looked at active CD patients (aCD, n = 30), CD patients in clinical remission (rCD, n = 20), Ulcerative Colitis (aUC, n = 11 and rUC, n = 13) patients and healthy subjects (HS, n = 15). Primary cultures of colonic biopsies were also examined from CD inflamed (CDinf, n = 8), non-inflamed (CDnon-inf, n = 7) and healthy mucosa (HCM, n = 8). ***Confirmation cohort*** : 74 CD patients in remission (CDAI < 150) were followed prospectively for 1 year or until relapse (CDAI > 150 with an increase of at least 70 points from baseline). The sIL1RII was measured using ELISA. Statistical analyses were performed using SPSS software.
Results. Circulating levels of sIL1RII were significantly decreased in rCD patients as compared to those of HS (16007 [9855-25507] *vs.* 20073 [14537-28505] pg/ml ; $p < 0.05$). This decrease was even more pronounced in aCD (12516 [6270-23996] pg/ml) as compared with rCD ($p < 0.05$) and HS ($p < 0.01$). No significant differences of sIL1RII were observed between aUC and rUC patients and HS (19888 [10986-29015] and 21479 [13734-41708] *vs.* 20073 [14537-28505] pg/ml, NS). In CD patients, circulating levels of sIL1RII were negatively correlated with CRP levels ($p < 0.001$) and CDAI ($p < 0.05$). Soluble IL1RII secretion was lower in CDnon-inf ($p < 0.05$) and CDinf ($p < 0.01$) mucosa than in HCM. Interestingly, this lower levels was associated with a higher IL-1 levels in CDinf than in HCM and CDnon-inf ($p < 0.01$ and $p < 0.01$ respectively).
Confirmation cohort : Among the 74 patients who were prospectively followed, thirty three patients (45 %) relapsed. For those who relapsed, baseline sIL-1RII levels (median 15,216 [285-35,725] pg/mL) differed significantly ($P < .0001$) from levels measured upon relapse (median 592 [115-2757] pg/mL).
Conclusion : CD is associated with a dysregulated production of sIL1RII. Serum sIL-1RII is a strong marker of disease activity in Crohn's disease. Deficiency in sIL1RII may be essential to CD pathogenesis.

- L 04 -

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 (1), V. Bours (3), M. Malaise (2), P. Delvenne (4), E. Louis (1). (1) Service de Gastroentérologie, (2) Service de Rhumatologie, (3) Service de génétique, (4) Service d'anatomie pathologique, CHU Liège.

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 uninflamed 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.

- L 05 -

THE ROLE OF 4-1BB/4-1BBLIGAND COSTIMULATION IN IBD AND EXPERIMENTAL COLITIS. P. Maerten (1), C. Shen (1), B. Kwon (2), G. De Hertogh (1), P. Cadot (1), D. Bullens (1), L. Overbergh (1), R. Mittler (3), H. Heremans (1), G. Van Assche (1), K. Geboes (1), P. Rutgeerts (1), J. Ceuppens (1). (1)Leuven ; (2) Korea ; (3) Atlanta.

Many costimulatory receptor-ligand pairs are expressed in inflamed gut tissue from Crohn's disease (CD) patients and probably play an important role in the pathogenesis of the disease. Among these, the 4-1BB/4-1BBLigand (L) receptor-ligand pair has not been studied yet. 4-1BB/4-1BBL interaction is involved in T cell cytokine secretion and proliferation and has a role in experimental models such as arthritis and encephalitis.
The aim of the present study was to analyse whether 4-1BB/4-1BBL interactions are involved in the immune response in CD and the T cell transfer model of colitis. By immunohistochemistry and at mRNA level, we were able to show that 4-1BB and its ligand were expressed in inflamed (and to a lesser extend non-inflamed) gut tissue from CD patients. This finding was specific and not just a sign of inflammation, since 4-1BB expression was much lower in inflamed tissue from patients with ulcerative colitis. 4-1BB costimulation with agonistic anti-4-1BB antibody promoted proliferation of lamina propria T cells from inflamed CD tissue and stimulated these cells to produce IFN-g, which both may contribute to the inflammatory reaction present in inflamed CD tissue. A pro-inflammatory role for 4-1BB/-1BBL interaction in CD was further suggested in experimental colitis. We observed that scid mice reconstituted with naïve CD4+ T cells and treated with agonistic anti-4-1BB monoclonal antibody (mAb) developed more severe colitis compared to mice treated with control mAb. However, 4-1BB/4-1BBL interaction is not indispensable since 4-1BB deficient naïve CD4+ T cells induced colitis in recipient mice. Interestingly, these 4-1BB deficient CD4+ T cells induced colitis with a mixed Th1/Th2 cytokine pattern (in contrast to a Th1 pattern in mice reconstituted with wild type T cells) and lamina propria T cells from scid mice reconstituted with 4-1BB$^{-/-}$ CD4^{+} T cells were more susceptible to apoptosis compared to lamina propria T cells from scid mice reconstituted with wild type CD4^{+} T cells.
In conclusion, we found functional 4-1BB expression in CD and a role of 4-1BB/4-1BBL interaction in CD was underscored in experimental colitis.

- L 06 -

MYENTERIC GANGLIONITIS IN UNAFFECTED ILEAL SECTION MARGINS PREDICTS SEVERE AND EARLY POSTOPERATIVE CROHN-S DISEASE RECURRENCE. M. Ferrante, T. Hlavaty, G. De Hertogh, S. Vermeire, G. D'Haens, P. Rutgeerts, K. Geboes, G. Van Assche. Leuven.

Background : Although endoscopy allows detection of ileal recurrence in Crohn's disease (CD), it is a burden to the patient post-operatively. Histological markers predicting recurrence have not been identified despite routine analysis of resected segments. Preliminary data suggest that neural inflammation in proximal section margins predicts CD recurrence. The long term relevance of this finding however is unknown.
Aim : To assess the predictive value of neural lesions in ileo-colonic resection specimens for early endoscopic CD recurrence and for the long term re-operation risk.
Methods : Ileocolonic resection specimens and section margins of 59 CD patients were histologically scored for epithelial lesions, neural hyperplasia and the proportion of inflamed ganglia in both neural plexuses. Endoscopic recurrence was determined at 3 mths in all 59 and at 1 yr in 32 patients while no CD specific therapy was given. The pathologist (KG) was blinded for endoscopic and clinical outcome.
Results : One or more inflamed ganglia (defined as ganglionitis) in the myenteric plexus of the proximal section margins were present in 32/59 (54 %) of patients despite absence of epithelial lesions, but infrequent in the submucosal plexus and in colonic section margins. At 3 mths significant endoscopic recurrence (Rutgeerts score ^{3}2) was seen in 24/32 (75 %) of patients with compared to 11/27 (41 %) of patients without ganglionitis (OR 4.36 (1.44-13.23), p = 0.008) and at 1 yr in 14/15 (93 %) of patients with compared to 10/17 (59 %) of patients without ganglionitis (OR 9.80 (1.04-92.70), p = 0.041). The proportion of inflamed ganglia correlated with the severity of endoscopic recurrence at 3 mths (r = 0.252, p = 0.054) and 1 yr (r = 0.507, p = 0.003). The combination of ganglionitis and neural hyperplasia in the inflamed area (10/32) predicted 100 % endoscopic recurrence after 3 mths (OR 2.43 (1.38-4.29), p = 0.008). Ganglionitis did not correlate with time to re-operation (16 pts, means 7.0 vs 5.3 yrs, p = 0.174). Active or past smokers had a higher risk of early endoscopic recurrence (4/12 vs 23/31, OR 5.75 (1.36-24.39), p = 0.032), independent from ganglionitis in multivariate analysis.
Conclusions : Myenteric ganglionitis in the absence of epithelial lesions frequently occurs in proximal section margins and may serve as a surrogate predictor for post-operative recurrence, especially in combination with neural hyperplasia. We hypothesize that Crohn's disease may spread via the neural plexus of the gut.

- L 07 -

EFFECT OF PARASITE TREATMENT IN EXPERIMENTALLY INDUCED IBD IN RODENTS. T. Moreels, J. De Man, B. De Winter, P. Pelckmans Laboratory of Gastroenterology, University of Antwerp

Crohn's disease and ulcerative colitis are chronic relapsing inflammatory bowel diseases (IBD). Due to the fact that the pathogen causing IBD is still unknown, no causative treatment is currently available able to make the disease disappear. Recently, the hygiene hypothesis of the development of immunological diseases was proposed, stating that raising children in extremely hygienic environments with less exposure to parasite infections may negatively affect the development of the immune system, predisposing them to immunological diseases as IBD. This hypothesis is supported by experimental data showing that helminthic parasites protect against T helper 1 cell-mediated gastrointestinal inflammation like Crohn's disease. Both T helper 2 cells and regulatory T cells may be involved in this immunomodulatory mechanism. Here we review the experimental studies in rodents with different parasites in favour of the hygiene hypothesis, opening perspectives on new therapies for IBD.

- L 08 -

INTESTINAL HELMINTHS : A CLUE EXPLAINING THE LOW INCIDENCE OF IDIOPATHIC INFLAMMATORY BOWEL DISEASES (IBD) IN SUBSAHARIAN AFRICA? PATHOPHYSIOLOGICAL AND THERAPEUTIC PERSPECTIVES. R. Fiasse. Gastroenterology Unit UCL, Clin St-Luc.

Whereas the incidence of IBD, chiefly Crohn's disease (CD), has much increased in the West from 1950 to 2000, it remains low in Asia and subsaharian Africa. This is not due to genetic factors since immigrants from Asia and Africa acquire a greater risk for IBD in regions of high prevalence. The hygiene hypothesis suggests that the reduction of childhood infections in the West has increased the incidence of Th1-mediated diseases such as CD and of Th2-mediated diseases such as ulcerative colitis (UC) and allergic diseases, due to a lack of stimulation of regulatory (reg) T-cells which normally downregulate Th1- and Th2-mediated responses through production of IL-10 and TGF-β The "old friends" hypothesis supposes that saprophytic mycobacteria, lactobacilli and intestinal helminths are protecting against such immunodysregulation. Intestinal helminths are colonizing 1/3 of the world population, chiefly where IBD prevalence is low.They induce a Th2 response and a stimulation of reg T-cells. Experimental studies have shown that they reduce the severity of colitis induced by various toxic agents. Therefore trials with ingestion of innocuous ova of *Trichuris suis* were started. In 29 CD patients, a clinical response and a remission were observed after 23 wk in 79 % and 72 % of the patients, respectively ([1a]). In a randomized placebo-controlled trial in 54 UC patients ([1b]), a clinical response was observed in 43 % of the patients treated with *Trichuris suis* ova over 12 wk and 17 % of the patients treated with placebo ($p = 0.04$). There were no side effects. However, the benefit of chronic helminth infestation has been questioned in Ethiopian Jews (2). Compared with Israelis and «old» Ethiopian Jews previously dewormed, Ethiopian Jews recently arrived in Israel (85 % infested with helminths) had significantly reduced CD4/CD8 ratio of blood lymphocytes, as well as signs of chronic immune activation, impaired signal transduction and anergy. These abnormalities disappeared after deworming. If persistent, they may reduce the immunity against infections and protective immunity after vaccination ([2]). In conclusion, environmental factors in IBD are better understood but helminth therapy is still experimental. The absence of harmful effects on immunity should be evaluated at long term.

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- P01 -

DETECTION OF THE PROLIFERATIVE ZONE OF FOETAL CARDIAC-TYPE MUCOSA SUPPORTS THE CONTENTION THAT ADULT CARDIAC MUCOSA HAS A CONGENITAL ORIGIN. E. Pancken, G. De Hertogh, P. Van Eyken, N. Ectors, K. Geboes. Dpt. of Morphology & Molecular Pathology, University Hospital St.-Raphael, Minderbroedersstraat 12, 3000 Leuven.

Objectives : The precise nature of cardiac mucosa (CM) is unclear. It may be normal or metaplastic. If CM is native, its precursor should be present during gestation. In normal gastrointestinal mucosae, the epithelial proliferative zone has a constant location. If CM is normal, the proliferative zone of its precursor should also have a constant location. The aim of this study was to evaluate the foetal gastro-oesophageal junction (GOJ) for the presence of a precursor to CM and for the location of the epithelial proliferative zone in this precursor.
Methods : 26 autopsy specimens of the foetal GOJ (mean gestational age, GA : 22 w, range : 15-44 w) were step-sectioned and stained with haematoxylin and eosin to select sections showing the mucosal lining. The mucosae were classified in 6 types : multilayered ciliated and squamous epithelium ; and cardiac-, oxyntocardiac-, and fundic-type mucosa. The proliferative zone was detected by immunostaining (ABC method) for the Ki-67 antigen (antibody clone MIB-1, DakoCytomation). Staining was evaluated for location and compared between mucosal types.
Results : The proliferative zone of the multilayered ciliated epithelium (14-30 w GA) and of the squamous epithelium (from 34 w GA) was in the basal and parabasal cell layers (ANOVA-test, $p < 0.0001$). In all simple columnar epithelia, the crypts were composed of 3 compartments : an upper Ki-67 negative part with surface and pit epithelium, a middle Ki-67 positive part, and a deep Ki-67 negative part containing differentiating glandular cells. The number of cells staining for the Ki-67 antigen in the proliferative zone did not differ significantly between mucosal types (ANOVA-test, $p = 0.2329$). The number of cells in the glandular compartment of cardiac-type mucosa tended to increase throughout gestation (regression coefficient ?1 = 0.162).
Conclusions : Foetal cardiac-type mucosa showed a constant length and location of the Ki-67 positive proliferative zone throughout gestation, while the number of glandular cells tended to increase. Foetal cardiac-type mucosa therefore contained all the cell populations present in adult cardiac mucosa. These findings support the conclusion that adult cardiac mucosa has an identifiable precursor in the foetus.

- P02 -

UNUSUAL APPEARANCE OF A GASTROINTESTINAL STROMAL TUMOUR PRESENTING AS A LARGE EXOLUMINAL PEDUNCULATED CYSTIC TUMOUR OF THE STOMACH. V. Meert, F. Vandenbroucke (1), Y. Van Nieuwenhove (2), A. Hoorens. Department of Pathology, (1) Radiology and (2)Abdominal Surgery, AZ-VUB, Brussels, Belgium

In a 68-year-old man a large abdominal tumoral mass was discovered incidentally. Ultrasonography showed a well-defined large cystic mass with a diameter of approximately 13 cm in the right hypochondrium. Subsequent computed tomography and magnetic resonance imaging confirmed the presence of a large cystic lesion containing multiple contrast-enhancing septa and papillary projections. The tumour was adjacent to the right liver lobe, the stomach and the pancreatic head. However, no connection with any of these organs could be demonstrated. At laparotomy the mass was attached by a narrow stalk to the greater curvature of the stomach at the level of the antrum. The mass was resected along with a strip of the adjacent stomach wall. Grossly, the tumour had a smooth outer surface and measured 13×12 cm. On cut section it consisted of a unilocular cyst, filled with serous fluid. In the cyst cavity several membranous septa were present. The cyst wall was thin and measured 0.2 to 0.4 cm. Histologically it consisted of hyaline connective tissue with focal dystrophic calcifications. The pedicle of the tumour was in continuity with the muscularis propria of the stomach. Here the cyst wall was thicker and measured approximately 1.5 cm. It was made up of spindle cells organized in short fascicles. The spindle cells showed a light eosinophilic cytoplasm, vesicular nuclei and focally displayed prominent nuclear palisading. The mitotic count was less than 5 per 50 HPF. Immunohistochemically, the tumour cells showed a diffuse and strong positivity for c-kit (CD117) and CD34. A considerable part of the tumour cells were weakly positive for smooth muscle actin, but only rare tumour cells were desmin positive. S100 immunohistochemistry was negative. Areas of hydropic and myxoid degeneration were present, as well as signs of necrosis and haemorrhage with haemosiderin-laden macrophages and cholesterol clefts. The histological features and immunohistochemical profile of the tumour were consistent with gastrointestinal stromal tumour of intermediate to high risk. This case demonstrates that gastrointestinal stromal tumour with extensive cystic degeneration should be considered in the differential diagnosis of a cystic abdominal mass.

- P03 –

MATURE TERATOMA ARISING FROM AN ENTERIC DIVERTICLE IN A NEONATE WITH SPLIT NOTOCHORD SYNDROME. F. Stessels (1), M. Baldewijns (1), S. Robben (2), A. Van den Neucker (3), J de Haan (1), E. Heineman (4), A. Driessen (1). (1) Dept. of Pathology, (2) Dept. of Radiology, (3) Dept. of Paediatrics, (4) Dept. of Surgery, University Hospital Maastricht, The Netherlands.

The split notochord syndrome, described by Bentley and Smith in 1960, is a rare disorder, believed to be caused by an abnormal splitting of the notochord. The notochord is a cellular rod, which develops by transformation of the notochordal process during the third week of human development. Besides its role in the development of the axial skeleton, it is also involved in the differentiation of the endoderm of the gut. The split notochord syndrome encompasses a range of congenital malformations, including enteric or mediastinal cysts, combined with vertebral or spinal chord abnormalities. Enteric duplications and diverticula have also been described. We present a male in which defects of the thoracic vertebrae were accompanied by enteric duplications and a diverticle. This diverticle originated from the jejunum and extended through the diaphragm into the thorax. This intrathoracal mass was already diagnosed during prenatal examination. Postnatal radiological examination revealed an associated malrotation. A diagnosis of a bronchopulmonal foregut malformation was initially proposed, but because of the presence of vertebral anomalies a diagnosis of a split notochord became more likely. Three weeks after birth a surgical resection of this mass was performed because of a necrotising enterocolitis. Anatomopathological examination revealed a gastric ectopia, in the diverticle. Moreover in association with this gastric ectopia a mature teratoma was found in the top of this diverticle. The combination of a split notochord syndrome and a mature teratoma, which in this case consisted of different components of mesodermal and endodermal origin, is an extremely uncommon finding. This congenital tumour may have developed from dorsal enteric remnants, which may contain tissue derived from all three germ layers. Despite successful surgical intervention our patient died 4 months after birth because of progressive respiratory failure.

- P 04 -

GASTRIC CARCINOMA WITH OSTEOCLAST-LIKE GIANT CELLS AND LYMPHOEPITHELIOMA LIKE CARCINOMA OF THE STOMACH : TWO OF A KIND ? S. Willems (1), F. Carneiro (2), K. Geboes (3). (1) Leiden ; (2) Porto ; (3) Leuven.

Neoplasms with giant cells are mainly reported in soft tissue and bone. Primary gastric localisation is particularly rare with only 5 cases reported in the literature. These tumours are characterized by the presence of so-called osteoclast-like giant cells intermixed with the malignant cells and lymphoid stroma. The giant cells are called osteoclast-like because these tumours are more common in bones. Although some authors claim they might represent a distinct entity, several studies have demonstrated that the multinucleated giant cells are of monocytic/histiocytic origin and probably represent a host response to the accompanying neoplasm. Many other tumours are associated with an inflammatory infiltrate or lymphoid stroma. Some present particular microscopic features. An example of them is the lymphoepithelioma-like carcinoma described in the colon, bladder, liver, skin and oral cavity. These tumours appear as poorly differentiated adenocarcinomas accompanied by an abundant lymphoid stroma. Studies showed the presence of Ebstein Barr Virusin few gastric cases of lymphoepithelioma-like carcinomasuggesting a possible role for Ebstein Barr Virusinfection in their development. We report three additional cases of primary gastric carcinomas with strong lymphoid infiltrate (one with osteoclast-like giant cells and two lymphoepithelioma like carcinomas). All cases were morphologically similar. They were composed of poorly differentiated adenocarcinoma accompanied by an abundant lymphoid reaction. The only difference was the presence of giant cells in one case. We compared our cases with the cases of gastric carcinomas with osteoclast-like giant cells, reported in the literature. Since immunohistochemical-staining patters were completely similar, showing no malignant character for the lymphoid cells nor for the giant cells, we think that the presence of these cells is a secondary event. Moreover, based on morphology, immunohistochemistry, detection for microsatellite-instabilityand the presence of Epstein Barr Virus, we think that gastric carcinomas with osteoclast-like giant cells and lymphoepithelioma-like carcinomas of the stomach might represent the same entity.

- P 05 -

PATHOLOGICAL RESPONSE IN RECTAL CANCER AFTER A COMBINATION OF RADIOTHERAPY WITH OXALIPLATIN AND CAPECITABINE. S. Aydin (1), JP. Machiels (2), P. Scalliet (3), Y. Humblet (2), A. Kartheuser (4), R. Detry (4), C. Sempoux (1). (1) Dept of Pathology ; (2) Dept of Medical Oncology ; (3) Dept of Radiotherapy ; (4) Dept of Surgery, Cliniques Universitaires Saint-Luc, 1200 Brussels, Belgium.

Local recurrence after surgery is a cause of treatment failure and relapse in patients with locally advanced rectal cancer (LARC). Preoperative radiotherapy has been shown to significantly decrease the local recurrence rate ([1]) and the potential benefit of adding chemotherapy is currently under investigation ([2]). We compared two different regimens of preoperative radiochemotherapy in term of pathological response. Thirty-six patients with LARC (T3-T4 and/or N+ staged by endorectal US) receiving radiotherapy (1.8 Gy, 5 days/week, 5 weeks, total dose 45 Gy, 3D conformational technique) in combination with i.v. oxaliplatin 50 mg/m^2 once weekly and oral capecitabine 825 mg/m^2 twice daily on each day of radiation were compared to 35 patients (matched for age and stage) treated with the same radiation regimen but with 5-Fluorouracil alone as radiosensitizer. In both groups, surgery was performed 6-8 weeks after completion of radiotherapy. The efficacy was assessed by the pathological response following Dworak's ([3]) and Wheeler classifications ([4]). Complete pathological response (complete disappearance of tumor cells) was observed in 5 patients (14 %) in the oxaliplatin group and in 4 (11.4 %) in 5-FU group. Good regression according to Dworak was found in 6 (18%) additional patients in oxaliplatin group and in 6 (17.1 %) in 5-FU group. Following the Wheeler classification, good regression was observed in 21 (58%) in oxaliplatin group and in 21 (60 %) in 5-FU group. Clearance of the circumferential resection margin ([5]) existed in 30 patients (83 %) treated with oxaliplatin regimen and in 31 patients (88.6 %) treated with the 5-FU. Combining preoperative radiation with oxaliplatin and capecitabine in patients with LARC results thus in significant tumor downstaging. Compared with our control group, pathological responses did not seem to be significantly improved by this new regimen. This analysis is limited by the small number of patients and its retrospective nature and should be confirmed in large randomized phase III.

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- P 06 -

INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS OF THE PANCREAS : VALUE OF PREOPERATIVE EUS-GUIDED FNAB FOR THE DIAGNOSIS OF MALIGNANCY. C. Sempoux (1), C. Galant (1), P. Deprez (2), I. Borbath (2), J. Gigot (3), B. Weynand (1). (1) Dept of Pathology, Cliniques Universitaires Saint-Luc ; (2) Dept of Gastroenterology, Cliniques Universitaires Saint-Luc ; (3) Dept of Surgery, Cliniques Universitaires Saint-Luc.

Intraductal papillary mucinous neoplasms (IPMN) of the pancreas is a recently described entity characterized by focal or diffuse duct ectasia together with neoplastic epithelial proliferation ranging from benign to high grade dysplasia with or without associated invasive adenocarcinoma ([1-4]). One of the most difficult problems in this entity is to predict the presence of a malignant component ([5]). We investigate the accuracy of the pre-operative EUS-guided FNAB in terms of diagnosis and assessment of malignancy. Between May 2002 and May 2004, 11 patients (6 men, median age : 61.8 years and 5 women, median age : 57.8 years) underwent pancreatic surgical resection for IPMN and had a pre-operative EUS-guided FNAB. On the surgical specimen, 8 cases were malignant showing either high-grade dysplasia (focal in 4 cases and diffuse in 1 case) or already infiltrating carcinoma (3 cases). Two were classified as borderline IPMN and one as IPMN adenoma. In 9 patients (82 %), FNAB was positive for IPMN and it was non informative in 2 (18%), one corresponding to the IPMN adenoma and the other one to a IPMN with invasive carcinoma. By FNAB, malignancy was diagnosed in 3/9 cases (38%), one corresponding to IPMN with invasive carcinoma, one to IPMN with diffuse high-grade dysplasia and the last to IPMN with focal high-grade dysplasia. For the diagnosis of malignancy, the sensitivity of FNAB is 38% and the specificity 100 %. The positive and negative predictive values are 100 % and 38% respectively. The accuracy is 55 %. In conclusion, EUS-guided FNAB is an excellent tool to confirm the diagnosis of IPMN but it often underestimates tumour grade.

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Invited lecture

- P 07 -

THE HISTOPATHOLOGY OF COELIAC DISEASE. V.VILLANACI,Brescia, ITALY

Coeliac disease (CD) has a wide range of clinical presentations and has been diagnosed with increasing frequency in patients in their 4th and 5th decades of life. The diagnosis of CD is confirmed by a combination of clinical, serological and morphological findings associated with a response to a gluten free diet. The gold standard of diagnosis remains the small-bowel mucosal biopsy. The histological diagnosis of coeliac disease in routine practice is based on a correct orientation of the biopsies of the duodenum (a minimum of 4 biopsies, 2 in the distal and 2 in the proximal duodenum) and on the classification of Marsh modified by Oberhuber and a new proposed classification. The pathological evaluation, in the initial lesions, is strictly related to a precise count of the number of the intraepithelial lymphocytes in the superficial epithelium with the aid of an immunohistochemistry stain with CD3 monoclonal antibodie for T lymphocytes. The pathologist's role is to give the clinician a precise evaluation of the situation of the duodenal mucosa without a diagnosis of coeliac disease that remains to the clinician on the base of clinical, laboratory and a correct histopathological evaluation. The pathologist, furthermore, plays an important role in the diagnosis of some complications of the disease as Refractory CD the so called Collagenous sprue, the Ulcerative Jejunitis and Intestinal T cell Lymphoma and also in the differential diagnosis with Autoimmune Enteropathy, Tropical sprue, Common Variable Immunodeficiency, Infectious Enteritis due to Giardia or viruses and Food protein intolerance.

- P 08 -

INFLAMMATORY BOWEL DISEASE AND COEXISTENT BIOPSY-PROVEN RENAL PATHOLOGY : A REPORT OF 19 CASES. E. Lerut (1), B. Maes (2), B. Van Damme (1), N. Ectors (1). (1) Department of Pathology, University Hospitals Leuven, Minderbroedersstraat, 12, B-3000 Leuven. ; (2) Department of Nephrology & Transplantation, University Hospitals Leuven, Herestraat, 49, B-3000 Leuven.

Background : Secondary amyloidosis has been recognized as an extraintestinal manifestation of IBD, being more frequent in Crohn's disease (CD) (0.9 %) than in ulcerative colitis (UC) (0.07 %). Most of these patients have renal involvement. Coexistent IBD and glomerulonephritis, however, is rare. To our knowledge, only 25 cases have been reported worldwide of which 9 were diagnosed as IgA nephropathy.

Study population and results : We present a population of 19 patients (10F/9M) with a history of IBD as well as biopsy-proven renal pathology. Fifteen patients were diagnosed with IBD before developing renal disease. This was neither specifically associated with the type (11CD/4UC), nor with the activity nor with the duration of the IBD (2 months-30 years). Renal diagnoses were varied : 6 cases of IgA nephropathy (4CD/2UC), 5 cases of renal amyloidosis (5CD/0UC), 3 cases of focal IgA-negative glomerulonephritis (1CD/2UC) and 1 case of hemolytic uremic syndrome (1CD/0UC). One CD+IgA nephropathy patient and 1 CD+renal amyloidosis patient developed PSC later on. Three patients had primary renal failure prior to the diagnosis of IBD (2CD/1UC). In all 3 cases IBD was diagnosed 3 years after the renal biopsy. Two patients with IgA nephropathy were later diagnosed with CD. One of them underwent a renal transplantation later on, in which he developed recurrent IgA nephropathy. One patient with a membranous glomerulonephritis developed UC and relapsed in his membranous glomerulopathy afterwards. One patient presented with a non-caseous granuloma in the renal biopsy at the time of diagnosis of CD.

Discussion : Our population contributes to the rather limited literature data that IBD and renal involvement are linked. The majority of our patients were diagnosed with IBD before developing renal disease. Besides amyloidosis, IgA nephropathy appears to occur with IBD. The pathogenesis of the latter link, however, remains speculative.

- P 09 -

EMBRYOLOGICAL REMNANTS OF DEVELOPMENT OF THE HIND- AND FOREGUT. A. Mathieu (1), J. Van de Stadt (1), J. Closset (1), P. Golstein (1), F. Le Moine (1), G. Klöppel (2), I. Salmon (1), N. Nagy (1). (1) Erasme (ULB) ; (2) Kiel.

The embryological development of the hindgut and foregut may be responsible of persistance of embryological remnants. We report two different cases of such lesions. The first case is a tailgut cyst associated with a carcinoid tumor in a 49-year old woman who presented during a few months a sensation of rectal fullness with irregular emission of mucus. Magnetic resonance imaging showed a retrorectal well-circumscribed cystic mass. The microscopic examination revealed a cystic lesion lined with a variety of epithelia including squamous, columnar and transitionnal. In the cystic wall a carcinoid tumor was developed. Tailgut cysts are uncommon congenital abnormalities which arise in the presacrococcygeal space occuring in adult patients. Differential diagnosis included rectal duplication, cystic sacrococcygeal teratoma, epidermal cyst, epidermoid cyst, anal duct or gland cyst. In the literature we could identified 18 other cases of malignancy including 6 carcinoid tumors. The second case is a pancreatic ciliated foregut cyst developed in a 26-year old woman who presented intense epigastric pain. Magnetic resonance imaging showed a cystic lesion in the pancreatic tail of 54 mm diameter containing homogenous material compatible with a mucinous cystadenoma. Microscopic examination revealed a cystic lesion lined by ciliated columnar epithelium supported by fibrous tissue. Pancreatic cysts included pseudocysts and various benign and malignant cystic lesions. Although extremely rare (6 cases have been described in the literature), ciliated foregut cysts must be added to the list of pancreatic cystics lesions and considered in the differential diagnosis with other cystics lesions such as mucinous cystic tumor.

- P10 -

MULTILOCULARIS ECHINOCOCCHUS INFECTION : CASE REPORT AND LITTERATURE REVIEW. M. Vivario (1), P. Vermeulen (2), M. Van Severen (2), C. Jardon-Jeghers (1), J. Demonty (5). (1) Laboratoire d'Anatomie Pathologique CDV Rue Du Parc 27 4800 Verviers ; (2) CHPTL Rue Du Parc 29 4800 Verviers ; (5) CHU Bat B35 4000 Liege

We present clinical, radiological and histological aspects of a multilocularis echinococchus infection (alveolar hydatidosis) case with hepatic and pulmonary lesions. A 65 year old man, blackberries eater and treated for a myelomonocytic leukemia, presents a right hypochondrial pain. In two years, a few small hepatic cysts evolve in a voluminous multilocular mass of 23 centimeters with multiple pulmonary nodules. Hepatic, epiploic and lung nodules biopsies show an intense granulomatous and necrosing reaction with eosinophils. Round structures limitated by a strongly PAS positive cuticle, evoke a parasitic infection. Serology for echinocchus multilocularis stays negative for a long time and becomes positive later.The patient is medically treated.Alveolar echinococcosis is a mainly hepatic, zoonotic parasitic disease caused by the larval stage of the fox tapeworm Echinococcus multilocularis.Adult worms mature in the intestine of the definitive host (usually fox) and the eggs are released in the feces. Accidental ingestion of soil, berries or vegetables contaminated with eggs initiate the infection of humans. Oncospheres hatch in the duodenum, penetrate the intestine and are carried through the bloodstream to organs. The main site of development is the liver. In Belgium, endemic areas of fox infection predominate in the Ardennes. In untreated cases, alveolar Equinococchosis has a high mortality rate. Surgical removing is the first treatment but is not always possible. Drugs can stop the development of the parasite.

- P11 -

IMPROVEMENT OF EUS-GUIDED PANCREATIC FINE-NEEDLE ASPIRATION RESULTS WITH INTRODUCTION OF THE MONOLAYER TECHNIQUE. B. Weynand (1), I. Borbath (2), C. Sempoux (1), C. Galant (1), J. Gigot (3), P. Deprez (2). (1) Service d'anatomo-pathologie ; (2) Service de gastro-entérologie ; (3) Service de chirurgie digestive, Cliniques universitaires St-Luc, Université Catholique de Louvain, avenue Hippocrate, 10, 1200 Bruxelles.

Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) has been performed in our institution for 8 years, mainly focusing on pancreatic lesions. As from mid 2002, the cytology laboratory introduced the monolayer technique (Thermoshandon's Papspin) for cervical smears and by extension to non-gynaecologic specimen.
Aim : to evaluate the impact of monolayer technique introduction on EUS-FNA diagnostic accuracy in pancreatic solid masses.
Methods : retrospective review of all pancreatic FNA performed before (year 2000), during (2002-2003) and after (2003-2004) monolayer technique introduction. Final diagnosis was obtained by surgery or clinical follow-up > 6m and consisted in adenocarcinomas, neuroendocrine tumors, intraductal papillary mucinous tumors (IPMT) and 1 cystic and pseudopapillary tumor. FNA was performed with 22G needles, with no on-site pathologist present.
Results (shown in table) : A significant drop in non-contributory specimens, from the second year of use of the new technique (*, $p < 0.05$). Most of these specimens were neuroendocrine tumors and IPMTs and were due to adequate sampling difficulties. From mid 2003, a significant improvement of sensitivity, accuracy and NPV was observed ($, $$, $p < 0.05$) that compares favourably to published data when on-site pathologist is present. Monolayer technique improved the results by reducing hemorrhagic background, by a better fixation (immediate immersion of material in the fixative), concentration of material by centrifugation and possible ancillary techniques such as immunohistochemistry on cell blocks.

Table	**2000**	**2002-3**	**2003-4**
N	80	98	106
Non-contributive FNA (%)	15	10.9	4.5*
Sensitivity (%)	81	82.5	94.7$
Specificity and PPV (%)	100	100	100
NPV (%)	51	76	88
Accuracy (%)	88	88.7	96$$

Conclusion : the monolayer technique led to a significant improvement of sensitivity, accuracy and NPV in EUS-FNA for pancreatic solid masses, although a learning period was needed both for the cytologist and the endoscopist. These results prove that very accurate results can be obtained without on-site pathologist.

- P12 -

FOCAL TTF-1 EXPRESSION IN GASTRO-ESOPHAGEAL JUNCTION ADENOCARCINOMAS AND SURROUNDING NON-NEOPLASTIC MUCOSA IMPINGES ON ITS SPECIFICITY FOR LUNG ADENOCARCINOMAS AND THYROID LESIONS. H. Alaerts (1), A. Driessen (2), E. Verbeken (1), K. Geboes (1), T. Lerut (5), N. Ectors (1). (1) Department of Pathology, University Hospitals Leuven, Minderbroedersstraat, 12, B-3000 Leuven. ; (2) Department of Pathology, Univesity Hospital Maastricht, P. Debyelaan 25 Postbus 5800, AZ 6202 Maastricht, The Netherlands ; (5) Department of Thoracic Surgery, University Hospitals Leuven, Herestraat, 49, B-3000 Leuven, Belgium.

Tumoral lesions, especially mucus secreting adenocarcinomas, of various origin, may demonstrate extensive morphological similarities and thus raise diagnostic problems especially when considering metastatic deposits. Markers such as cytokeratins, hormone receptors are used for the distinction between different sites of origin. The diagnostic value and especially the specificity of these markers is variable. TTF-1 (thyroid transcription factor-1) has been detected in more than 90 per cent of pulmonary small cell carcinomas and in 75 percent of pulmonary non-small cell carcinoma resulting in a high sensitivity and specificity. However, an occasional report suggested cross-reaction with other tumors. Coincidental demonstration of TTF-1 expression in an esophageal adenocarcinoma prompted us to investigate this finding. A representative paraffin block from 65 resection specimens for gastro-esophageal junction adenocarcinomas was investigated by means of immunohistochemistry. The patients (M/F 6.1 ; mean age : 64 yrs) were treated by primary surgery. Semi-serial sections were stained with H&E and TTF-1 (Novocastra, monoclonal antibody, dilution 1/50). All sections were selected to contain tumor, 47 slides did contain normal esophageal mucosa, 30 normal gastric mucosa and 18 Barrett's mucosa. The analysis of the slides demonstrated focal nuclear expression of TTF-1 in 6 out of 64 tumors (9.39 %). In 13 out of 30 samples of normal looking gastric mucosa (43.33 %) few deeply seated glands were positive. The gastric mucosa did not show distinctive inflammatory changes, nor metaplastic changes. Barrett mucosa and normal squamous mucosa were negative in 100 %. In conclusion, it appears that TTF-1 is rather sensitive and specific as a marker for lung cancer but mucus secreting cells of other origin may also express TTF-1. Since the positivity is rather focal the clinical implications of this finding are mainly limited to small samples i.e. diagnostic forceps and punction biopsies. The distribution of positive glands in the deep glandular parenchyma of the mucosa of the proximal part of the stomach raises questions concerning the type and origin of these glands. A metaplastic origin has to be considered.

- P13 -

COLORECTAL STUMP AS A MAJOR RISK FOR COLORECTAL CANCER IN CROHN'S DISEASE. I. Bueres Dominguez (1), C. Sempoux (2), R. Fiasse (1), R. Detry (3), A.Geubel (1), O.Dewit (1). (1) Gastroenterology, (2) Pathology and (3) Colorectal Surgery Departments. UCL Saint Luc.

Background and aim : in Crohn's colitis and ulcerative colitis, screening for dysplasia and/or colorectal cancer (CCR) is advocated for diseases of 8 to 10 years duration. In addition, colon exclusion with stomy may be required in emergency surgical management of Crohn's disease (CD) but dysplasia and CCR have been only rarely described in patients with longstanding colorectal stump.
We **report the cases** of 2 patients who developed a few years after surgery three CCR in the excluded colorectal stump. Patient 1 is a 80-year-old man with CD for 5 years complicated by ileo-sigmoido-vesical fistulae that required a right hemicolectomy, sigmoidectomy and transverse colostomy. No follow-up was done because of the lack of compliance. He remained asymptomatic during 5 years under sulfasalazine therapy. After 5 years he exhibited hematochezia. A flexible endoscopy showed a rectal tumor of 9 cm in diameter and biopsies showed a picture of a poorly differentiated adenocarcinoma with transmural invasion and signet ring cells. A few days later the patient unfortunately died of pneumopathy prior to surgery. Patient 2 is a 88-year-old man with Crohn's disease since the age of 28, time of his first ileocolonic resection. Forthy-five years later, due to the presence of several colonic and rectal benign stenosis, an ileostomy was performed. He was then lost for follow-up. Fifteen years after the ileostomy, he presented with hematochezia and the coloscopy showed two different tumors : one in the upper part of the rectum and another one 15 cm above the rectosigmoid junction. A colectomy was peformed and confirmed the existence of two separate cancers (both mucoid adenocarcinomas T3N0). Interestingly the whole colonic mucosa showed mild to severe dysplasia. The patient died 3 years later. Conclusion These caricatural cases outline the high CCR risk in patients with colorectal stump ; the latest representing another risk group additive to that of patients with other risk factors such as cholangitis or familial history of intestinal neoplasia. The diagnosis is unfortunately often delayed because of the screening difficulties in these asymptomatic patients. In patients with colorectal stumps, coloproctectomy should be performed if reanastomosis is no longer considered. A second choice strategy should include an annual or biannual endoscopic surveillance with multiple biopsies to guide the decision of proctectomy.

- P14 -

GROOVE PANCREATITIS-ETIOPATHOLOGICAL CONSIDERATIONS. K. Wetzels (1), R. Aerts (2), W. Van Steenbergen (3), C. Verslype (3), D. Bielen (4), D. Vanbeckevoort (4), N. Ectors (1). (1) Department of Pathology, University Hospitals Leuven, Minderbroedersstraat, 12, B-3000 Leuven ; (2) Department of Abdominal Surgery, University Hospitals Leuven, Herestraat, 49, B-3000 Leuven ; (3) Department of Liver, Gallbladder and Pancreatic diseases, University Hospitals Leuven, Herestraat, 49, B-3000 Leuven ; (4) Department of Radiology, University Hospitals Leuven, Herestraat, 49, B-3000 Leuven.

Chronic pancreatitis is a fibroinflammatory disease that is induced by injuries to the different components of the parenchyma i.e. the interstitial, ductal, and/or acinar cells. The most important causes of chronic pancreatitis are alcohol abuse, gene mutations, autoimmune processes, special anatomic changes, and obstructive duct lesions. The morphologic spectrum of the various types of chronic pancreatitis may show features that allow an etiological distinction. "Groove pancreatitis" is a special form of segmental chronic pancreatitis affecting the "groove" between pancreatic head, duodenum and common bile duct. This type of chronic pancreatitis was first described by Becker in 1973 and is mainly coined in the German literature and more recently the Asian literature. In groove pancreatitis, the pancreatic duct system is grossly normal, calcifications or intraductal protein plugs being rare. Very commonly, scarring of the duodenal wall, stenosis of the duodenum, true duodenal wall and pancreatic cysts are detected. Cystic dystrophy on aberrant pancreas of the duodenal wall was described in 1970 by Potet *et al*. This condition starts off as a congenital default, which in time will be complicated by inflammatory changes situated in the "groove" between pancreatic head and duodenum causing a segmental chronic pancreatitis i.e. "groove pancreatitis". Most of the articles published on this entity originate from France. We reviewed 11 cases of groove pancreatitis diagnosed on Whipple resection specimens. The majority of the cases had been operated for suspected pancreatic carcinoma. The patients were predominantly young men (M/F : 9/2 ; mean age 47 yrs, range : 41-53). All resection specimens were characterised by the presence of cysts, necrosis and alterations of the muscularis propria of the duodenum. In more than half ectopic pancreatic glands were retrieved in the duodenal wall. The pancreatic ducts contained inspissated secretions - protein plugs - in the majority of cases. The Brunner glands appeared hyperplastic in all cases, although to a variable extend. In view of a potential etiopathogenetic mechanisms the Brunner gland hyperplasia appeared not to be (invertedly) correlated to the presence of ectopic pancreatic glands. Although, at least one of the changes was always present.
In conclusion, from this morphological review it would appear that the changes described at operation are complex and especially variable. Part of it probably relates to the previous history of episodes of pancreatitis. In a number of cases some changes may be indicative of an underlying mechanism. In few cases, no clear cause of events could be traced.

Invited lecture

- P15 -

CLASSIFICATION OF PANCREATIC INTRAEPITHELIAL NEOPLASIA AND INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS : AN OVERVIEW OF RECENTLY PROPOSED REVISED DEFINITIONS AND DIAGNOSTIC GUIDELINES. A. Hoorens. AZ-VUB, Department of Pathology, Brussels, Belgium.

The majority of pancreatic neoplasms shows a ductal phenotype and can be classified as ductal adenocarcinomas. It is thought that they develop from preinvasive precursor lesions arising in the ducts of the pancreas. A classification system was developed for these precursor lesions : the pancreatic intraepithelial neoplasia (PanIN) system. It distinguishes between three grades of pancreatic intraepithelial neoplasia (PanIN-1, 2 and 3). The system allowed molecular analyses that have helped to define a progression model for pancreatic neoplasia. Molecular studies revealed that genetic alterations in PanIN-2 and PanIN-3 lesions are more related to invasive carcinoma than in PanIN-1. Intraductal papillary-mucinous neoplasia (IPMN) is a clinical and pathologic entity that is distinct from PanIN. IPMNs are divided into benign, borderline, and malignant non-invasive and invasive lesions. It is thought that these lesions spread slowly over the ductal system, with eventual progression in some cases to invasive carcinoma. A growing body of molecular and clinical evidence also supports this progression model for IPMN. A meeting of international experts on precursor lesions of pancreatic cancer was held at The Johns Hopkins Hospital, from August 18 to 19, 2003. The purpose of this meeting was to reach an international consensus on the diagnostic criteria for precursor lesions in the pancreatic ducts, PanINs and IPMNs. The revised definitions of PanINs and IPMNs will be reviewed and the differences from mucinous cystic neoplasms will be highlighted. Hruban R.H. *et al*. Am. J. Surg. Pathol. 2004, 28 : 977-987 Klöppel G., Luttges J. Curr. Gastroenterol. Rep. 2004, 6 : 111-118

Invited lecture
- R 01 –

GASTRO-ENTERIC AND PANCREATIC NEUROENDOCRINE TUMOURS. P. Smeets, Ph. Duyck. Dept. of Radiology & Medical Imaging, Ghent University Hospital.

Carcinoid tumours were first described by Oberndorfer in 1907 to distinguish them from true carcinomas. Now carcinoids are considered to be part of the neuroendocrine tumours (NETs). The NETs are defined by a common phenotype which is characterized by the expression of general markers such as Neuron Specific Enolase, Chromogranin, Synaptophysin and products of hormone secretion. These tumours may be localized in any part of the body. Among *endodermal NETs*, the most common localisations are the lungs, ileum, appendix, rectum and pancreas.
There may be an association with genetic conditions such as multiple endocrine neoplasia type 1 (MEN-1). Carcinoid tumours have an annual incidence of between 2 and 7 cases per million of population. Other neuroendocrine tumours are rarer : Insulinoma : 2 pmpy, Gastrinoma (Zollinger Ellison syndrome) : 1 pmpy, Vipoma : (Verner Morrison syndrome) : 1 p10mpy, Glucagonoma : 1 p20mpy, Somatostatinoma : 1 p40mpy. Patients with malignant neuroendocrine tumours have a relatively good prognosis compared to other malignancies, and may survive for many years. Morbidity from neuroendocrine tumours is either due to hormone production or to the bulk of the tumour and metastases, which can be extremely large. We discuss the classification and imaging characteristics of G-NETs and P-NETs. Ultrasound, CT and MR scanning and angiography all have a role to play in preoperative tumour localisation. Nuclear medicine using either labelled octreotide or MIBG is also useful in localising primary and secondary carcinoid and other neuroendocrine tumours.

- R 02 -

PROGNOSTIC VALUE OF CT IN ISCHEMIC COLITIS. E. Danse, B. Van Beers, A. Kartheuser, P. Laterre, O. Dewit, L. Goncette. St Luc University Hospital, UCL, Brussels.

Aim : To evaluate the prognostic value of CT in ischemic colitis, compared with early laboratory findings and age.
Subjects and Methods : We reviewed the early laboratory datas (leucocyte count), age and CT findingsof 19 consecutive patients with colitis. The patients were divided in three groups based on their outcome, the first group comprised the patients with transient ischemia withuneventfull recovery, the second group included the patients who needed surgery because of delayed colic stricture and the third group included the patients who needed early surgery because of symptomatic transmural colic gangrene. Laboratory values and age were compared to CT fndings based on the classification of Balthazar (Radiology, 1999), including type A (inhomogeneous thickening of the colic wall and pericolic fatty tissue infiltration), type B (moderate homogeneous thickening without change of the pericolic fat) and type C (thin wall with colic pneumatosis).
Results : Spontaneous resolution was noted in nine patients ; complicated form was noted in 10 patients (two fibrotic strictures and eight necroses). Resolution was noted in five types A and four types B. Fibrosis was noted in one type A and one type B. Necrosis was noted in two types A, two types B and in four types C. Leucocyte count was higher in necrosis (19.10^3 elts/mm^2) than in the two others situations (13 and $14.5.10^3$ elts/mm^2 respectively in transient ischemia and fibrosis). Mean age was higher in fibrosis (78.5) and necrosis (75) than in spontaneous resolution (57).
Conclusion : The more severe forms of ischemic colites are observed when CT findings demonstrate thin colic wall with pneumatosis and in older patients.

- R 03 -

INTUSSUSCEPTION IN ADULTS : VALUE OF CROSS-SECTIONAL IMAGING. M. Spinhoven (1), B. Op de Beeck (1), F. Deckers (2), K. de Jongh (1), P. Parizel (1). (1) Universitair Ziekenhuis Antwerpen ; (2) Sint Augustinus Ziekenhuis Wilrijk.

Purpose : To present a pictorial review of the different etiologies of intussusception in adults and their imaging characteristics, mainly focused on cross-sectional imaging.
Methods and Materials : Imaging findings of 15 cases of surgically proven intussusceptions in adults were reviewed. All patients underwent at least a CT-scan examination. All CT examinations were conducted on a spiral unit with administration of both oral and intravenous contrast. Site, level, cause and degree of obstruction as well as signs of threatened bowel viability were evaluated and correlated with surgical findings and pathology examination.
Results : The etiologies of the small bowel intussusceptions were : celiac disease ([2]), Meckel diverticulum, lipoma, leiomyoma, post-operative adhesions, metastasis lung carcinoma and melanoma. Large bowel intussusceptions were due to : colon carcinoma ([2]), caecum carcinoma, appendiceal mucocele, fibroid polyp, non-Hodgkin lymphoma and angiolipoma. Most relevant cross-sectional imaging findings were : a target or doughnut lesion, or a reniform or sausage-shaped mass when observed in the longitudinal axis. Between these layers, there is usually an area of fat representing invaginated mesentery, with blood vessels and sometimes lymph nodes.
Conclusion : Intussusception in adults is a rare pathological finding, but becoming more frequently in day-to-day radiological practice. Radiologists should be familiar with the imaging characteristics and look for the underlying cause.

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- R 04 -

MASSIVE BENIGN PNEUMATOSIS INTESTINALIS : A RADIOLOGICAL CHALLENGE. L. Trappeniers (1), F. Vandenbroucke (1), K. Martens (3), C. Ernst (1), T. Stadnik (1). (1) AZ VUB, Brussels,Belgium, Dep. Radiology ; (3) AZ VUB, Brussels, Belgium, Dep. Surgery.

Pneumatosis cystoides intestinalis is a rare condition characterized by multiple subserosal or submucosal gas filled cysts within the wall of a segment of the bowel. It is associated with a numerous conditions of either intra- or extra-abdominal origine. The patient can be asymptomatic or may present symptoms like nausea, vomiting, diarrhea or other signs of intestinal obstruction. In a patient with vague clinical presentation the radiological findings, sometimes associated with pneumoperitoneum, can lead to a clinical dilemma, due to the fact that most patients have comorbid conditions wich are also associated with intestinal perforation. The autors present the case of a 40 year old woman who was transferred to our emergency for abdominal distention and suspicion of pneumoperitoneum on a radiography of the abdomen. A massive pneumatosis of the entire bowel associated with a small amount of free intraperitoneal air was found in this patient. The authors will highlight the importance of recognizing pneumatosis intestinalis as a possible mimic of free intraabdominal air as well as a possible cause of benign pneumoperitoneum.

- R 05 -

QUANTIFICATION OF THE STIMULATING EFFECT OF SECRETIN WITH MRCP ON PANCREATIC EXOCRINE FUNCTION. M A Bali, A Stzantics, M Arvanitaki, J Devière, C Matos. H Erasme, ULB, Bruxelles.

Background : Secretin is a gastrointestinal hormone that stimulates acinar and ductal pancreatic cells to produce bicarbonates-rich fluid. Tests exploiting this physiologic phenomenon have been developed in the attempt to detect pancreatic exocrine dysfunctions. Magnetic Resonance Cholangio-Pancreatography (MRCP) is a non-invasive diagnostic technique, now used in routine, able to quantify pancreatic exocrine function by measuring pancreatic fluid output and total excreted volume after secretin stimulation.
Purpose : To evaluate the stimulating effect of two different doses of secretin 1 and 0.3 clinical unit (CU) by quantifying pancreatic exocrine flow output and total excreted volume with secretin-enhanced MRCP (S-MRCP).
Materials and Methods : 10 healthy volunteers (5M, 5 F, age range 22-29 years) after a fasting period of at least six hours underwent S-MRCP. Each S-MRCP was repeated two times for each dose of secretin (1 or 0.3 clinical unit per Kg of body weight) for each volunteer. The S-MRCP consisted in a dynamic, coronal multislice turbo spin-echo, heavily T2-weighted, with fat-suppression. The acquisition time for each dynamic was 12.5 sec within a single breath-hold. After the first dynamic acquisition, 20 mg of an antiperistaltic drug (Hyoscin butylbromide) was injected intravenously followed by the bolus of secretin. Thirty dynamic acquisitions were repeated at intervals of 30 seconds for 15 minutes. The quantification method was based on an individual calibration procedure providing a linear relationship between MR signal intensity and volume of the gastro-intestinal fluid. For this purpose, six additional acquisitions were performed in the same scan after ingestion of 120 mL of water administered in 6 increments of 20 mL. Pancreatic flow output and total excreted volume were derived from a linear regression between MR calculated volumes and time.
Results : For all examinations a linear increase of pancreatic exocrine fluid volume was observed. A statistically significant difference was found between pancreatic flow output ($p = 0.03$) and total excreted volume ($p = 0.002$) obtained for the two doses of secretin.
Conclusions : S-MRCP allows non-invasive quantification of pancreatic exocrine function. These results demonstrate that secretory capabilities of the exocrine pancreas are related to secretin dosage regimen

- R 06 -

NEED FOR OPTIMISING CLINICAL TNM-CLASSIFICATION IN PANCREATIC CANCER ? L. Delrue, V. Casneuf, P. Demetter, Ph. Duyck, B. de Hemptinne, M. Peeters, Pancreatobiliary Study Group.

Purpose : The purpose of this study was to evaluate the radiological TNM-classification (2002) versus the pathological classification in pancreatic cancer.
Materials and methods : Ninety-eight consecutive patients, who underwent a intentive curative resection for a clinical suspicion of malignancy during last decade, were evaluated. All had a pathologically proven adenocarcinoma of the pancreas. Their CT-scans were retrospectively analysed. If an MRI-scan was available, this was also reviewed. A clinical TNM-classification based on radiology was assigned. An independent pathologist redefined the TNM-classification in these patients. These findings were compared.
Results : Of 74 T-status, defined by imaging techniques, only 67 could be correlated with the golden standard of pathology. 35 (52.2 %) were concordant. Of 64 N-status, 45 (70.3 %) were concordant with the pathological N-status. For T-status, Spearman correlation coefficient showed a statistically significant correlation ($r = 0.28$; $P < 0.05$). For N-status, Spearman correlation coefficient showed poor correlation ($r = 0.362$; $P < 0.01$).
Conclusion : For T-classification : of the 20 patients who were clinically overstaged, 9 were assigned as T4 for a pathological T3, because vascular involvement cannot be assessed due to the surgical procedure (arterectomy was not performed). Is the distinction between T3 and T4 based on arterial invasion appropriate or should perineural invasion better be used as criterion ? The poor correlation of N-status can be partially explained by the scan technique : some of the CT-scans had a slice-thickness of 10 mm.

- R 07 -

ASSESSMENT OF DIFFUSION-WEIGHTED MRI IN LIVER FIBROSIS. L. Annet, F. Peeters, L. Hermoye, J. Abarca, V. Lebrun, I. Leclercq, B.E. Van Beers. Saint-Luc University Hospital, Brussels

Purpose : To assess the potential role of diffusion-weighted MRI to detect and grade liver fibrosis.
Animals and Methods : Liver fibrosis was induced in 15 rats by intraperitoneal CCL4 injection during 5 weeks (N = 6) or 9 weeks (N = 9). Diffusion-weighted MRI was performed in the 15 rats with liver fibrosis and in 10 normal rats. An echoplanar sequence was used with two b-values (0 and 500 s/mm^2) in three orthogonal directions to obtain the mean apparent diffusion coefficient (ADC). Imaging was performed in the living rats with cardiac and respiratory triggering and was repeated immediately after killing the rats. The hydroxyproline content of the liver was quantified in 13 rats (4 normal, 4 $CCL4_{5sem}$, and 5 $CCL4_{9sem}$).
Results : The ADC decreased significantly in relation with CCL4 induced fibrosis time in living rats (controls : 1535 ± 294 mm^2/s, $CCL4_{5sem}$: 1129 ± 273 mm^2/s, $CCL4_{9sem}$: 943 ± 132 mm^2/s, p = 0.003). No significant difference of ADC was observed between normal and fibrotic livers in the dead rats. A significant correlation was observed between hydroxyproline and ADC in the living rats (r = -0.692, p = 0.009), but not after death (r = 0.28, p = 0.354).
Conclusion : Decreased ADC correlated with increased liver fibrosis only in living rats, but not after death. Therefore, the decrease of ADC cannot be explained by decreased diffusion in liver fibrosis. Other factors, such as a decrease of perfusion may explain the apparent decrease of diffusion in living rats with liver fibrosis.

- R 08 -

TUBERCULOUS FOCAL SPLENIC LESIONS : MR IMAGING FEATURES. T. Van der Zijden (1), A. De Backer (2), F. Vanhoenacker (3), K. Mortelé (4), P. Parizel (5). (1) Department of radiology Ziekenhuis netwerk Antwerpen, Stuivenberg, Antwerp, Belgium, and University Hospital of Antwerp, Belgium ; (2) Department of radiology Ziekenhuis netwerk Antwerpen, Belgium ; (3) Department of radiology AZ Sint-Maarten, Belgium ; (4) Department of Radiology Division of abdominal imaging and intervention, Brigham and Women's hospital, Harvard Medical School, MA 02115, Boston, USA. ; (5) Department of Radiology University Hospital of Antwerp, Belgium.

Objective : The aim of this study was to describe the MR imaging features of tuberculous focal splenic lesions in patients with disseminated tuberculosis.
Subjects and Methods : MR imaging studies of eight patients with tuberculous focal splenic involvement were reviewed. The number, size, MR signal intensities compared to adjacent splenic tissue and patterns of contrast enhancement of tuberculous focal splenic lesions were evaluated. Splenic volume was also noted. In all patients manifestations of tuberculous involvement of other organs were tabulated.
Results : Tuberculous focal splenic lesions were nodular and multiple in all patients (mean : 16 ; range : 4-35 ; diffuse nodular involvement with an innumerable number of lesions was seen in one patient) and associated with splenomegaly (mean splenic volume : 472 cm3 ; range 302 - 876.5 cm3). On T2-weighted images iso-, hyper- and hypointense lesions were noted in 3 (37.5 %), 2 (25 %) and 2 (25 %) patients respectively. In one patient (12.5 %) combined hyper- and hypointense lesions were noted. On nonenhanced T1-weighted images lesions were hypo-, iso- and hyperintense in 4 (50 %), 3 (37.5 %) and 1 (12.5 %) patients respectively. On dynamic contrast enhanced images, two enhancement patterns were noted : gradual peripheral enhancement (GPE) and gradual enhancement with complete fill-in (GPE-CFI). GPE was noted in six (75 %) patients and GPE-CFI in 1 (12.5 %) patient. In one (12.5 %) patient lesions with both enhancement patterns were noted. Splenic lesions larger than 5 mm in diameter showed GPE pattern. GPE and GPE-CFI patterns were demonstrated with smaller lesions.
Conclusion : In our series, tuberculous focal splenic lesions are small, multiple and most often associated with splenomegaly. Signal intensities and patterns of contrast enhancement may vary both on T1- and T2-weighted images and reflect different stages of the tuberculous process. Lesions were best visualized on fat-suppressed contrast-enhanced T1-weighted images performed during the portal venous phase followed by the equilibrum phase, arterial phase and finally, T2-weighted and nonenhanced T1-weighted images. Two different enhancement patterns were noted, probably reflecting different stages of the pathologic process. A gradual peripheral enhancement pattern with central nonenhancing portion is highly suggestive for peripheral granulation tissue with central liquefaction or caseous necrosis. Peripheral enhancement pattern with complete fill-in on delayed images may reflect well-formed granuloma. The latter enhancement pattern has to the best of our knowledge not previously been described.

A 24-YEAR-OLD FEMALE PATIENT WITH ASPECIFIC ABDOMINAL PAIN AND UNEXPLAINED PERIODIC FEVER. H. Ashkzaran, P. Smeets, I. De Schrijver, L. Delrue, Ph. Duyck. Dept. of Radiology & Medical Imaging, Ghent University Hospital.

We report the case of a 24-year-old female patient with a large hepatic cyst-like mass. Ultrasound examination of the liver showed several possibly multilocular cystic masses at the hilar region with slight compression of the portal vein. MR investigation supported the cystic nature of the lesions though there appeared to be wall enhancement upon administration of gadolinium. To evaluate a suspected connection to the biliary tree a CT-scan after iv. infusion of cholangiographic contrast was performed and this confirmed appearance of bile in the larger cyst. The smaller cysts were considered classical biliary cysts. A histopathological diagnosis of epidermoid cyst of the liver was made on the enhancing larger cyst. The differential diagnosis of epidermoid cysts of the liver is broad and definitive diagnosis is only obtained upon pathological examination of the surgical specimen. Because of the potential for malignant degeneration, complete resection of the hepatic lesion must be obtained.

- T 01 -

ROLE OF NASAL POTENTIAL DIFFERENCE MEASUREMENT IN THE DIAGNOSIS OF IDIOPATHIC CHRONIC PANCREATITIS. P. Deprez (1), P. Lebecque (2), P. Wallemacq (3), JF. Gigot (4), Y. Horsmans (1), T. Leal (5). (1) Gastroenterology Dpt ; (2) Pediatry Dpt ; (3) Clinical Chemistry Dpt ; (4) Digestive Surgery Dpt ; (5) Clinical Chemistry Dpt, Cliniques universitaires Saint-Luc, Universite Catholique de Louvain, Av Hippocrate 10, 1200 Brussels.

Background : Idiopathic chronic or recurrent pancreatitis remains a clinical diagnostic challenge even in the era of molecular biology. Single allelic or compound heterozygous CFTR mutations have been associated with chronic idiopathic pancreatitis. Nasal potential difference (NDP) measurement has been proposed to assess defective ion transport in cystic fibrosis (CF).
Aim : evaluate NDP in patients with idiopathic pancreatitis and CFTR mutations and clarify the contradictory results obtained with NDP measures in the literature.
Patients and methods : pts with chronic pancreatitis, diagnosed by helical CT, MRI, EUS or ERCP, with no history of hereditary pancreatitis, alcohol intoxication or metabolic disease and presenting with a CFTR mutation, but no lung disease, were included. Five pts underwent endoscopic or surgical ductal drainage. Interestingly, 2 pts presented adenocarcinoma and 1 IPMT during follow-up of mean 6.8 y [range 2-14]. Two pts developed diabetes and 3 pts exocrine pancreatic insufficiency. NDP was measured with a simplified method based on nasal instillation in supine position at reduced flow rates (Leal 2003). These results were compared with those of CF pts (n = 21) and controls (n = 34).
Results : 10 patients (9 men,1 woman), mean age 32 years (24-59) presented for 3 of them a G542X mutation, 1 a R117H, 1 a DF508 and 4 an intron 8 “5T allele”. Mean sweat chloride values were normal : 28.7 mmol/L [range 11-49]. NPD measures showed normal baseline values (13.4 mV [7-20] vs 16.6 [7-31] in controls and 44.9 [16-62] in CF, and normal inhibition after instillation of amiloride in baseline solution. Significant decreases of voltage cumulative changes were however observed after instillation of low Cl^- solution plus amiloride : 4.9 [1-9] in patients vs 10.4 [3-17] in controls ($P < 0.001$) and 1.9 [-17-+19] in CF, and after low Cl^- solution instillation containing isoprenaline and amiloride 8.8 [0.5-18] vs 15.5 [7-31] ($P < 0.005$) in controls and 4.2 [-16-+26] in CF patients.
Conclusions : significant abnormal NPD values were observed after pharmacological stimulation in all patients evaluated for idiopathic chronic pancreatitis and heterozygous mutations of the CFTR gene. This reflects abnormal Cl^- secretion and could explain the pancreatic symptoms. This easy and inexpensive test should be proposed to these patients, before genetic testing, since mutational screening of the entire CFTR gene cannot be considered in every patient with idiopathic pancreatitis.

- T 02 –

IMPROVEMENT OF EUS-GUIDED PANCREATIC FINE-NEEDLE ASPIRATION RESULTS WITH INTRODUCTION OF THE MONOLAYER TECHNIQUE. B. Weynand (1), I. Borbath (2), C. Sempoux (1), C. Galant (1), J. Gigot (3), P. Deprez (2). (1) Service d’anatomo-pathologie, (2) Service de gastro-entérologie ; (3) Service de chirurgie digestive, Cliniques universitaires St-Luc, Université Catholique de Louvain, avenue Hippocrate, 10, 1200 Bruxelles.

Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) has been performed in our institution for 8 years, mainly focusing on pancreatic lesions. As from mid 2002, the cytology laboratory introduced the monolayer technique (Thermoshandon’s Papspin) for cervical smears and by extension to non-gynaecologic specimen.
Aim : to evaluate the impact of monolayer technique introduction on EUS-FNA diagnostic accuracy in pancreatic solid masses.
Methods : retrospective review of all pancreatic FNA performed before (year 2000), during (2002-2003) and after (2003-2004) monolayer technique introduction. Final diagnosis was obtained by surgery or clinical follow-up > 6m and consisted in adenocarcinomas, neuroendocrine tumors, intraductal papillary mucinous tumors (IPMT) and 1 cystic and pseudopapillary tumor. FNA was performed with 22G needles, with no on-site pathologist present.
Results (shown in table) : A significant drop in non-contributory specimens, from the second year of use of the new technique (*, $p < 0.05$). Most of these specimens were neuroendocrine tumors and IPMTs and were due to adequate sampling difficulties. From mid 2003, a significant improvement of sensitivity, accuracy and NPV was observed ($, $$, $p < 0.05$) that compares favourably to published data when on-site pathologist is present. Monolayer technique improved the results by reducing hemorrhagic background, by a better fixation (immediate immersion of material in the fixative), concentration of material by centrifugation and possible ancillary techniques such as immunohistochemistry on cell blocks.
Conclusion : the monolayer technique led to a significant improvement of sensitivity, accuracy and NPV in EUS-FNA for pancreatic solid masses, although a learning period was needed both for the cytologist and the endoscopist. These results prove that very accurate results can be obtained without on-site pathologist.

Table	**2000**	**2002-3**	**2003-4**
N	80	98	106
Non-contributive FNA (%)	15	10.9	4.5*
Sensitivity (%)	81	82.5	94.7$
Specificity and PPV (%)	100	100	100
NPV (%)	51	76	88
Accuracy (%)	88	88.7	96$$

- T 03 -

PANCREATIC CYSTIC LESIONS : DIFFERENT PROGNOSES. V. Casneuf, L. Delrue, P. Demetter, M. De Vos, B. de Hemptinne, M. Peeters. Ghent University Hospital.

Objectives : A retrospective analysis of disease free and overall survival of patients with benign and malign cystic lesions of the pancreas.
Methods : Identification of patients with a cystic lesion of the pancreas, referred to our hospital during the last ten years, by searching throughregistration systems of our hospital and medical files. Final diagnoses were based on pathologic data or long term clinical follow-up. Referring physicians were contacted for actual survival data when necessary.
Results : Forty-two patients were identified and could be followed up until death or until survival on October 2004. There were 20 adenocarcinomas with cystic components, 6 serous cystadenomas, 7 mucinous cystadenomas, 6 cystadenocarcinomas and 3 intraductal papillary mucinous tumours (IPMN). Seventeen of 20 adenocarcinomas underwent a R0 resection. This group has a mean disease free survival (DFS) of 20.6 months (range 2-92) and a mean overall survival (OS) of 27.7months (range 5-92). Three patients underwent a R1 resection for an adenocarcinoma, and had a mean OS of 9.3 months (range 6-14). Four of 6 serous cystadenomas underwent a R0 resection (of which 1 died immediately postoperative and is excluded from the analysis), 1 underwent enucleation, and 1 did not undergo surgery, because of old age (diagnosis is based on radiology and clinical follow-up). This group has a mean DFS and OS of 61.6 (range 28-150 months). All 7 mucinous cystadenomas underwent a R0 resection,with amean DFSof 71.0 months (range 15-144 months) anda mean OSof 81.4 months (range 53-144 months). All 6 cystadenocarcinomas underwent R0 resection, though 1 died immediately postoperative and was excluded from the analysis.Mean DFS in this group is 33.0 months (range 5-66 months) andmean OS is 39.2 months (range 12-66 months). Three patients with IPMN underwent a R0 resection. They have a mean DFS and OS of 15.3 months (range 2-40 months). When comparing DFS and OS between groups, the following significant differences were demonstrated : patients with mucinous cystadenomas had a significantly longer DFS in comparison to cystadenocarcinoma ($t = 2.25$, $P < 0.05$) and adenocarcinoma ($t = 3.8$, $P < 0.01$).OS for mucinous cystadenomaswas also significant different from cystadenocarcinoma ($t = 2.83$, $P < 0.05$) and from adenocarcinoma ($t = 4.78$, $P < 0.001$). **Conclusions** : This study demonstrates that patients with mucinous cystadenomas present a clinical subgroup, with a clear better prognosis than carcinomas. No differences were found between adenocarcinomas with cystic degenerationand cystadenocarcinomas. No differences were found between mucinous and serous cystadenomas.

- T 04 -

PANCREATITIS-INDUCED ARTERIAL COMPLICATIONS : RESULTS OF TRANSCATHETER EMBOLIZATION. G. Maleux (1), V. Goosens (2), S. Heye (3), G. Wilms (4), W. Van Steenbergen (5). (1) Radiology, University Hospitals, Leuven ; (2) Radiology, University Hospitals, Leuven ; (3) Radiology, University Hospitals, Leuven ; (4) Radiology, University Hospitals, Leuven ; (5) Hepatology, University Hospitals, Leuven.

Purpose : In a retrospective study, we evaluated the efficacy, safety, and long-term clinical outcome of pancreatitis-induced arterial complications managed by transcatheter embolotherapy.
Materials and methods : Between August 1992 and October 2004, 15 consecutive patients (12 men, 3 women) with a mean age of 53.8 yrs (range 38-69 yrs) underwent transcatheter embolization of a pancreatitis-related arterial complication. In 8 patients, the underlying disease was chronic pancreatitis, the remaining 7 patients suffered from acute pancreatitis. Pancreatitis was caused by alcohol abuse (n = 10), biliary stones (n = 2), post-ercp (n = 1), and was of unknown origin in one case. Indications for angiographic evaluation and subsequent transcatheter embolization were epigastric pain (n = 5), gastrointestinal haemorrhage (n = 3), retroperitoneal haemorrhage (n = 3), external haemorrhage via abdominal drain (n = 1), and asymptomatic CT-findings (n = 4).
Results : Selective visceral angiography revealed a pseudoaneurysm (n = 12), a pseudoaneurysm with clear contrast extravasation (n = 3), and an arteriovenous fistula (n = 1). Injured arteries were the gastroduodenal artery (n = 3), pancreaticoduodenal arcade (n = 5), middle colic artery (n = 1), splenic artery (n = 5), right hepatic artery (n = 1), and the left gastric artery (n = 1). Embolization was performed with different embolic agents : vascular coils (n = 10), microparticles (n = 2), glue (n = 1), glue and coils (n = 1), and microparticles, glue and coils (n = 1). One embolization session was performed in 12 patients ; the remaining 3 patients needed a second embolization within one week after the first session. In three patients intentional occlusion of the splenic artery resulted in partial splenic infarction. Clinical follow-up (mean period 56 months ; range 1_141 months) revealed no late recurrence of symptoms. Four patients (27 %) died during follow-up due to multiple organ failure (n = 1), acute pancreatitis (n = 1), suicide (n = 1), and cerebral haemorrhage (n = 1).
Conclusion : Transcatheter embolotherapy is a minimally-invasive but very effective and durable treatment modality to definitively manage arterial complications related to pancreatitis. Partial splenic infarction can occur and is directly related to the intentional coil-occlusion of the splenic artery. Twenty-seven percent of the patients died during further follow-up, not of bleeding but of a non-related condition.

ENDOSCOPIC TREATMENT OF EXTERNAL PANCREATIC FISTULAS. M. Arvanitakis (1), M. Delhaye (1), C. Matos (2), M. Bali (2), O. Le Moine (1), J. Devière (1). (1) Dpt of Gastroenterology, Erasme University Hospital ; (2) Dpt of Radiology, Erasme University Hospital.

Background : Endoscopic treatment by transpapillary main pancreatic duct (MPD) drainage has been proposed for the treatment of external pancreatic fistulas (EPF) when conservative measures fail. Technical success rate is 75 % and fistula closure is achieved in 80 % of cases. Additional endoscopic procedures, as transmural drainage of an associated pancreatic fluid collection (PFC) or of the MPD could also be useful when transpapillary MPD drainage alone is not optimal. The aim of the study was to assess the efficiency of combined endoscopic procedures in the treatment of EPF.
Patients and Methods : Nine patients with an EPF underwent endoscopic treatment in our department between 1997 and 2004. Four patients had chronic pancreatitis. EPF occurred after pancreatic surgery (n = 6), percutaneous drainage of a PFC (n = 2) and abdominal, non-pancreatic surgery (n = 1). The mean interval between the onset of EPF and treatment was 3.5 (1-18) months. Two patients had high output EPF (> 200 cc/day). Pancreatic duct disruption (PDD) was noted in all patients based on MRCP and/or ERCP findings and a PFC was present in 6. All patients but one had previous unsuccessful conservative treatment with somatostatin analogues. Endoscopic treatment with combined techniques was performed.
Results : All patients underwent transpapillary MPD drainage by pancreatic sphincterotomy, ductal stricture dilation if required (n = 2) and temporary nasopancreatic catheter insertion followed by MPD stenting (n = 2). Transpapillary MPD drainage was combined in 6 cases with the following endoscopic procedures : a) transmural PFC drainage by cystogastrostomy (n = 2), b) transmural drainage between the path of the EPF and the duodenum (n = 2) or the stomach (n = 1) followed by stent insertion (in these cases, an associated PFC could not be identified by EUS and the drainage was performed using the existing EPF path, from the exterior towards the digestive lumen) and c) EUS-guided pancreaticoduodenostomy with pancreaticoduodenal stent insertion, because of complete PDD (n = 1). The mean number of procedures was 2 (1-3).There were no complications. EPF closure was achieved in 8 patients in a mean interval of 15 (7-30) days. Two patients had EPF recurrence during a mean follow-up period of 17 (5-52) months requiring additional endoscopic treatment, with subsequent EPF resolution.
Conclusions : When transpapillary MPD drainage alone is inadequate for the management of EPF, combined endoscopic treatment is safe and effective.

VIDEO CAPSULE ENDOSCOPY IN SMALL BOWEL MALIGNANCY. D. Urbain. AZ VUB.

Small bowel (SB) malignancy is unfrequent and early diagnosis is crucial for therapy. The Video Capsule Endoscopy (CE) has improved the diagnosis of SB diseases, but data concerning the place of this technique in detecting SB malignancy are scarce and consist mostly in case reports or small series. A recent review of SB malignancy by collecting abstracts and studies mentioning SB malignancies as found by CE showed that the percentage of SB malignant tumors in the 892 patients collected was 3.8%. Capsule endoscopy was performed in 86.6 % for gastro-intestinal bleeding of undefined origin and/or iron deficiency anaemia ([1]). Some authors compared CE and Push Enteroscopy (PE) ([2]). While the number of collected cases of SB was tumors was in all series very limited, it appears that in some cases, tumors could be diagnosed by only one of the 2 techniques. Push enteroscopy is probably more reliable for proximal lesions, while CE is able to detect lesions located too far for PE. In a recent Belgian multicentric study, 2.5 % of 443 CE procedures showed SB tumors, most frequently adenocarcinomas. The real added diagnostic yield of CE was estimated to 1.6 % as comparedwith the classical work-up. The mean number of diagnostic procedures performed before CE was 3.6, mostly consisting in oesophago-gasro-duodenoscopy and colonoscopy. Larger prospective studies remain needed to better define the rule and the timing of CE in SB diseases, especially malignant processes.

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- X 01 -

A RANDOMIZED PLACEBO-CONTROLLED CLINICAL TRIAL OF PROBIOTICS (L. JONHSONII, LA1®) ON EARLY ENDOSCOPIC RECURRENCE OF CROHN''S DISEASE (CD) AFTER ILEO-CAECAL RESECTION. A. Van Gossum (1), O. Dewit (2), K. Geboes (3), F. Baert (4), M. De Vos (5), E. Louis (6), M. Enslen (7), M. Paintin (7), D. Franchimont (1). (1) ULB Erasme - Brussels ; (2) UCL Saint-Luc - Brussels ; (3) KUL Gasthuisberg - Leuven ; (4) HH Ziekenhuis - Roeselaere ; (5) UZ Gent ; (6) CHU Sart Tilman - Liège ; (7) Nestle Research Center Lausanne.

Rationale : A 70 % of patients exhibit recurrent endoscopic lesions within 1 year demonstrating early and rapid relapse of intestinal inflammation after surgery. This study was designed to assess the effect of an oral administration of probiotics for preventing early post-operative recurrence of CD.
Patients and Methods : Patients with CD were pre-operatively enrolled when scheduled for ileocaecal resection and were randomly assigned after surgery to daily treatment of either L. jonhsonii La1®, Nestlé (1010 CFU) (group A) or a placebo (group B) for 12 weeks. No other medication was allowed during this study period. ***Design*** : a multicenter, prospective, randomized, placebo-controlled clinical trial. Stratification was performed according to current smoking status at the time of randomization. All the data were considered in an *intention-to-treat* (ITT) *model* and a *per-protocol* (PP) *analysis*.
Objectives : The primary objective was to assess the effect of La1® on the endoscopic relapse rate *(Rutgeerts score : i0 to i4)* at week 12. The secondary objectives evaluated the histological score *(Geboes score),* clinical relapse rate (CDAI), serum CRP level, safety and tolerance.
Results : Seventy patients (33 females-37 males ; mean age at onset : 26 ± 9 years ; mean age at randomization : 37 ± 13 years ; 87 % suffering from a fibrostenotic disease (B2)) were enrolled with 34 patients assigned to group A and 36 to group B. The mean endoscopic score was not different between group A and group B at week 12 (1.44 ± 1.31 vs 1.05 ± 1.21, respectively ; NS). The percentage of patients with mild (i1+i2) or severe endoscopic recurrence (i3+i4) was not significantly different between the 2 groups (Mild : A = 45.2 % vs B = 39.3 %, NS ; severe : A = 27.9 % vs B = 33 %, NS). At week 12, there was no difference between the 2 groups for the following : histological score, CDAI and serum CRP level. The Pearson correlation coefficient between the histological and endoscopic score was equal to 0.496 (p = 0.0003). Forty-nine patients were considered in the PP analysis which showed similar results. Tolerance was similar in both groups. There was no serious adverse event probably related to the treatment in group A, but one in group B.
Conclusion : Oral administration of La1® in patients with CD failed to prevent early endoscopic recurrence at 12 weeks after ileo-caecal resection. No therapeutic gain was observed on histological score, clinical relapse or CRP level. Administration of La1® was considered to be safe.

- X 02 -

IRON INTAKE AND STATUS IN ADULT BELGIAN WOMEN. I. Pynaert, C. Matthys, M. Bellemans, M. De Maeyer, S. De Henauw. Department of Public Health, Ghent University, Belgium.

Objective : To describe the iron intake and iron status and to study their association in adult Belgian women.
Subjects : Adult women (18-39 years) from the region of Ghent were examined in the year 2002.
Methods : The iron intake was determined on the basis of a newly developed and validated computerised iron intake assessment tool (IIAT). To determine the iron status the following indicators were measured : haemoglobin, haematocrit, RBC, serum iron, transferrin, ferritin and soluble transferrin receptors (sTfR). Pearson correlation coefficient was used to evaluate the association between iron intake and status.
Results : The mean (± S.D.) total iron intake in adult women (n = 796) was 10.4 (± 3.33) mg/day. Haem and non-haem iron intake were respectively 0.7 (± 0.50) mg/day and 9.6 (± 3.22) mg/day. A proportion of 99 % of the women had a total iron intake below the Belgian Recommended Dietary Allowance. The food groups with the highest mean proportional contribution to total iron intake were : bread (19.3 %), meat and meat products (12.3 %), cereals (11.7 %) and vegetables (10.8%). The mean values (± S.D.) for the indicators of iron status in adult women (n = 778) were : 13.5 (± 1.00) g/dl haemoglobin, 40.9 (± 3.62) % haematocrit, 4.5 (± 0.49) × 10^6/µl RBC, 99.0 (± 41.62) µg/dl serum iron, 2.8 (± 0.50) g/l transferrin, 37.9 (± 35.11) ng/ml ferritin and 1.2 (± 0.39) mg/l sTfR. Iron deficiency (ferritin < 12 ng/ml) was seen in 15.6 % of the women and iron deficiency anaemia (ferritin < 12 ng/ml and haemoglobin < 12 g/dl) in 2.1 %. Pearson correlation coefficient for total iron intake and ferritin was 0.031 and for total iron intake and sTfR -0.019 (n = 736).
Conclusions : The total iron intake in adult Belgian women is considerably lower than the current recommendations. However, this is not reflected in the iron status, for which better results are seen. Moreover, no correlation is found between the iron intake and status.

- X 03 -

CURRENT PRACTICE OF GLYCEMIA CONTROL IN EUROPEAN INTENSIVE CARE UNITS. Ph . Devos, J-Ch. Preiser. Soins Intensifs Généraux C.H.U. Sart Tilman.

Current practice of glycaemia control in intensive care units (ICUs) could have been influenced by the seminal work of Van den Berghe *et al.* published in 2001, that reported an increased survival in surgical critically ill patients by intensive insulin therapy titrated to keep blood glucose between 80 and 110 mg/dL. These data were confirmed in 2003 by Finney *et al.* in another unicentric trial performed in a similar population with a glycaemia threshold of 150 mg/dL. As these findings can hardly be extrapolated in other populations of ICU patients or in ICUs using different standards of management, the comparison of these glycaemia thresholds in a multi-centre trial is warranted. We performed a survey among ICUs that could be interested in a multi-centre study (named Glucontrol). The participants were surveyed over their data collected in 2003. A total of 33 ICUs (610 beds and 30894 admissions in 2003) were screened. Most of these ICUs are medico-surgical (n = 25), while medical and surgical ICUs are less common (n = 5 and 3). Mean ICU mortality rate and length of stay were 13.4 ± 9.4 % and 7.1 days ± 3.0 days, respectively. Median APACHE II Score was 17.65 (range : 10 to 30). The threshold for glucose correction was standardised for any type of patients in 31 ICUs : 110 mg/dl (n = 3), 120mg/dl (n = 5), 150 mg/dl (n = 15), 180 mg/dl (n = 5) and 200 mg/dl (n = 3). In the 2 last ICUs, two thresholds (110 or 150 mg/dl) were used according to the underlying pathologies. Most ICUs (n = 28) used a standard protocol of insulin. 27 ICUs used continuous intravenous insulin infusion if necessary while 6 ICUs did not. 14 ICUs also use subcutaneous administration of insulin during ICU stay while 19 ICUs do not. Glycaemia is most often checked each 6 hours (n = 20), sometimes each 4 hours (n = 8) and rarely each 3, 8, 12 hours (n = 2, 2, and 1).
In conclusion, there is a large heterogeneity in the management of glycaemia in Europeans ICUs. This may be explained by the absence of recommendations based on a multi-centre, large-scale, randomised trial in a heterogeneous population of intensive care unit patients.

Invited lecture

- X 04 -

THE FOR COELIAC DISEASE ICEBERG SCREENING : YES OR NO ? S. Salvatore. Università dell'Insubria, Varese, Italy.

Coeliac disease (CD) is a genetically-based immune-mediated chronic gluten intolerance, with a worldwide increasing prevalence, currently estimated to affect 0,5-1 % of the general population. In the past, CD was considered a rare disorder mainly affecting infancy, characterized by chronic diarrhoea with malabsorption and impaired growth. In the last 20 years, a broad spectrum of clinical and sub-clinical manifestations of CD has been discovered thanks to improved serological screening. The alterations may involve the liver, heart, thyroid, pancreas, skin, bone, neurological and reproductive systems and may appear at any age without any overt intestinal signs. High sensitive and specific serological tests are now available (antiendomysial and human tissue transglutaminase antibodies) that reliably (positive predictive value of 98-100 %) select cases to submit intestinal biopsy to confirm diagnosis. Life-long gluten free diet (GFD) permits healing of enteropathy, normalisation of antibodies and complete resolution of symptoms and signs. An early diagnosis of CD seems also essential to reduce the risk of complications such as autoimmune related disorders, osteoporosis, infertility and, possibly, risk of cancer in symptomatic patients with intestinal atrophy. On the contrary, the long-term benefit of a strict diet in asymptomatic patients (recruited by screening in at-risk groups of population) or patients with slightly abnormal biopsies (increased lymphocyte infiltration without atrophy - Marsh I) still need to be further elucidated. Furthermore the improvement of quality of life on diet is somehow counteracted by (still too) relevant social and cost-related difficulties in daily life.

- X 05 -

CELIAC DISEASE : IS A DUODENAL BIOPSY STILL NEEDED TO CONFIRM POSITIVE SEROLOGICAL TESTS ? F. Mascart, A. Ocmant, I. Beukinga. Lab Immunol. Hôp. Erasme, U.L.B., Brussels.

The gold standard criterium for the diagnosis of celiac disease is a small-intestinal histology showing villous atrophy. However, in view of the variable clinical presentations of gluten intolerance, with numerous sub-clinical disease, a small intestinal biopsy cannot always be proposed as a first diagnostic test, so that less invasive serological tests have been developed. The need for an histological confirmation of the positive serological tests depends on the specificity of these tests. The most recommended serological test is actually the search for anti-endomysium (EmA) or anti-transglutaminase (TTG) IgA in serum, combined with a determination of IgA concentration. We have developed and are now validating a still less invasive test allowing the determination of anti-TTG IgA in saliva. Both the sensitivity and the specificity of anti-EmA IgA have been limited by the need of a specific technical skill to correctly detect these antibodies. However, in reference laboratories, similar results are obtained by detecting anti-EmA or anti-TTG IgA. In such reference laboratories, specificity of both tests is excellent so that one can really question in these conditions the need for a confirmatory intestinal biopsy. Histological diagnosis of atypical cases is indeed not always easy, and the quality of the histological specimens is often poor so that the diagnosis of celiac disease should actually not depend only on biopsy. In contrast, as serological tests are not 100 % sensitive, partially as a consequence of the prevalence of IgA deficiency among celiac patients, an intestinal biopsy should be proposed in any clinical suspicion of celiac disease with negative serological tests. In case of doubtful or negative histological result, a further evaluation of the percentage of gd cells within the intra-epithelial mucosal lymphocytes as well as a HLA-DQ analysis should be proposed. We conclude that it is probably time to change the diagnostic criteria for celiac disease and this should be further discussed.

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- X 06 -

CELIAC DISEASE : A POLICY-MAKER'S VIEW. A. De Swaef, Headpharmacist-director. Belgian Institute for Health and Disability Insurance.

Celiac disease occurs in approximately 20.000 Belgians. A person who has the disease must take up a special diet that contains no gluten. Foodstuffs that contain no gluten are generally speaking more expensive than normal foodstuffs. Taking all this into account, the Belgian institute is investigating a possible reimbursement for these products. This decision will be based on therapeutic, social and economic criteria as is required by Belgian law. If and when a reimbursement will be instated it will be fixed as a lump sum. The following questions, amongst others, will have to be answered during the evaluation process : what is the prevalence, who will diagnose the disease, which diagnostic tests have to be used, cost of the gluten-free foodstuffs. Finally the legislation that might be the result of this evaluation has to pass various committees and authorities that have to authorise the proposal before it can be enacted.

RISK STRATIFICATION FOR COLORECTAL CANCER SCREENING. S. Tejpar. KUL, Leuven, Belgium.

In addition to the well-recognized syndromes described (FAP, HNPCC) clusters of colorectal cancers occur in families much more often than would be expected by chance. Postulated reasons for this increased risk include `mild' and undetected mutations of APC and mismatch repair genes, as well as yet unknown polymorphisms in genes involved in nutrient or carcinogen metabolism. This familial clustering in about 10-20 % of colorectal cancers has implications for screening because the immediate family members of a patient with apparent sporadic colorectal cancer have a twofold to threefold increased risk of the disease. The magnitude of the risk depends on the age at diagnosis of the index case, the degree of kinship of the index case to the at-risk case, and the number of affected relatives. Thus, in addition to screening the easily identifiable high-risk groups such as FAP and HNPCC, care should be taken to recognize intermediate-risk patients and to provide them with appropriate screening recommendations (figure 1). Because the molecular basis and the natural history of these intermediate-risk patients is largely unknown, screening recommendations are as yet more empirical. Future research into the molecular basis of these syndromes should allow more definite risk evaluation. Screening strategies have been developed to address the familial risk of commonly observed colon cancer. Screening recommendations are empiric and combine the known effectiveness of available screening tools with the observed risks associated with family history. If a person has a first degree relative with colon cancer, average risk colon cancer screening is commended, but starting at age 40 years. The decreased age is given because the risk at age 40 years for those with an affected first-degree relative is similar to the risk at age 50 years for the general population. An individual with two first-degree relatives affected with colon cancer or one first-degree relative diagnosed under the age of 60 years should have colonoscopy beginning at age 40 years, or 10 years younger than the earliest case in the family. Colonoscopy should be repeated every five years if negative. An even stronger family history of colon cancer syndromes of colon cancer.should suggest the consideration of one of the inherited syndromes.

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PRO SCREENING : LESSONS FROM THE UK SIGMOIDOSCOPY TRIAL.

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Both incidence and mortality from colorectal cancer (CRC) are theoretically preventable by screening since extensive evidence suggests that advanced and frequently fatal CRCs develop during an asymptomatic phase from early, localised and therefore treatable cancers, which in turn develop from benign adenomatous polyps. The average time for an early, asymptomatic cancer to become symptomatic is thought to be around 2-3 years and for an adenoma to progress to carcinoma around 10 years. These lag times offer ample time for a screening intervention.
Flexible sigmoidoscopy (FS) allows direct examination of the mucosa of the sigmoid colon and rectum where 60 % of colorectal cancers and adenomas are located. Satisfactory bowel preparation for FS can be achieved with a single enema that can be self-administered at home. Evidence from case-control and cohort studies indicates that screening by sigmoidoscopy reduces incidence and mortality rates of distal CRC. However in the absence of evidence from randomised trials, most countries have been unwilling to introduce endoscopic screening. Four randomised trials are in progress (in UK, Italy, US and Norway 1-4). Although the US recommends a 5 yearly screening interval, the protection afforded by a single FS may last for up to 10 years or even longer depending on the age at which it is undertaken. The UK and Italian trials are examining the effectiveness and duration of protection of a single FS screen undertaken between age 55-64. Both trials have completed recruitment and screening and the participants are being followed up using national cancer registries. It is expected that the first results on incidence rates for both trials will be available in 2008.
The UK Sigmoidoscopy Trial is the largest of the trials and has already yielded important results on the feasibility, safety and acceptability of FS as a screening method. This trial recruited 194,726 men and women, aged 55 to 64 years, who had responded to a questionnaire and expressed an interest in having an FS screen. One third were randomly assigned to the FS screening group of whom 71 % underwent screening ; the remainder was assigned to a control group which was not contacted. Small polyps were removed during the screening FS and colonoscopy was performed only if high risk polyps (three or more adenomas, size 1 cm or greater, villous, severely dysplastic or malignant) were found. Of the 40,674 people who had the FS test, 5 % were classified as high risk and were offered colonoscopy (94 % accepted) ;

and the remaining 95 % were discharged. 62 % of the cancers detected at screening were at Dukes' Stage A (this compares with 40 % with the fecal occult blood test (FOBT), suggesting the FS detects cancers early than FOBT. Results of our trial and subsequent research suggest that sigmoidoscopy screening is remarkably safe : there was only a single perforation in the 40,000 participants who had a total of 19,000 polyps removed during screening. It is also highly acceptable, with 67 % of an unselected UK population attending for screening. We also demonstrated that it would be feasible to offer a single FS to the whole UK population, probably by having nurses undertake the procedure. We are also examining the possibility that non-medical pathologists would undertake classification of any polyps removed.
If the UK Sigmoidoscopy Trial demonstrates that FS screening is as effective as published evidence would suggest, then it is likely that a single FS screen would be offered to the whole population. This will require an increase in manpower and currently we are addressing training and resource issues.
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- S 03 -

SCREENING FOR COLORECTAL CANCER WITH FAECAL-OCCULT-BLOOD TESTS : TRIAL EVIDENCE AND BEYOND. J. Faivre. Dijon, France.

Colorectal cancer is one of the most common cancer in developed countries. Despite advances in diagnosis and therapeutic methods, its prognosis remains relatively poor. Faced with this disquieting situation, considerable research efforts have been made over the last 20 years to evaluate the ability of screening procedures to decrease the mortality or incidence of colorectal cancer. Currently, the simplest and most evaluated screening method for colorectal neoplasia is periodic stool testing for occult blood, followed by a colonoscopy in those screening positive. The most extensively evaluated test is a guaiac test intended to detect peroxydase-like activity of hemoglobin. The test is easy to perform (two small samples are collected from three consecutive stools), without great inconvenience to the individual and inexpensive. There are three European population-based trials and a US study among volunteers which compare colorectal cancer mortality within a study group and a control group. They provide very similar results. They reported a 14 % to 18 % reduction of colorectal cancer mortality in the general population with non-rehydrated Hemoccult II repeated at least every 2 years in asymptomatic adults aged 50 to 74 and with a medium follow-up of 10 years. In participants or volunteers mortality reduction varied from 33 % to 39 %. A decrease in colorectal cancer incidence was reported in the US study after 18 years of follow-up. Available data suggests that the degree of reduction in mortality depends mainly on the compliance to the screening test, the number of screenings that the subjects participate in and of compliance of positive screens with the diagnostic follow-up colonoscopy. If compliance is low, no reduction of colorectal cancer mortality will be seen, even with a very effective test. In Nordic countries and in England, a high compliance rate was obtained with the mailing of the test with eventually one or two reminders. In France, this strategy resulted in low compliance. It has to be combined with the participation of primary care physicians who give the test to their patients over a period of 4-6 months. It is then mailed to non-consultants. The active participation of primary care physicians can be a major determinant of effectiveness in many countries. It has also been shown that this colorectal cancer screening strategy meets commonly accepted criteria for cost-effectiveness. The Advisory Committee on Cancer Prevention of the European Union and the European Commission have recently recommended the implementation of colorectal cancer screening with faecal occult blood tests. They also concluded that immunological tests, flexible sigmoidoscopy and colonoscopy cannot, at present, be recommended for population screening. Colorectal cancer screening was also included in the European Code against cancer. An organisation with a call-recall system and quality assurance evaluation is necessary in order to achieve effectiveness. The benefits of a screening programme are achieved only if compliance to the screening test is over 50 % initially and during successive screens and if a colonoscopy is performed in case of positive test. The positivity rate of the non rehydrated Hemoccult test without diet restriction is 2 % on initial screen and 1 to 1.5 % in subsequent screenings. The specificity of the test is 98 %, the sensitivity estimated to be between 50 and 60 % and the positive predictive value is around 10 % for cancer and ranges between 30 and 40 % for adenomas. Taking into account the EU recommendations, a national policy was decided in France. It was concluded that there was

unequivocal evidence that repeated faecal occult blood testing reduces colorectal cancer mortality in asymptomatic subjects over 50. Organisation rules were proposed by the Ministry of Health and 22 areas, covering 25 % of the population, were selected on their ability to organise the screening programme. A rigid organisation with a call-recall system and quality insurance was set up in each administrative area. The time has come to implement well-organised population-based faecal occult blood screenings despite current limitation of available tests. Efforts should be continued to improve faecal occult blood tests.

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- S 04 -

WHAT SHOULD WE PROPOSE TO THE AVERAGE RISK PERSON ?
PRO COLONOSCOPY

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In the western industrial countries, colorectal carcinoma (CRC) is one of the leading causes of death from cancer. About 60.000 new diagnoses and 30.000 deaths from CRC per year are the corresponding figures for Germany. It is well known for years, that CRC evolves from premalignant adenomas within a period of approximately 10 years. This process can be stopped by early polypectomy of adenomas. In addition it could be proved that the detection of CRC at an early stage (UICC I) is associated with a significantly higher rate of complete remission and longer survival compared to progressive stages. People at higher risk for adenomas and/or malignant transformation could be identified (e.g. Patients with HNPCC, FAP, family history for CRC or with previous polypectomy). Thus, screening strategies for CRC were developed, and especially the faecal occult blood test (FOBT) proved to be very efficient (Evidence grade I). Since this test only detects bleeding polyps or tumors, and small polyps – although premalignant – usually do not bleed, endoscopic screening methods were introduced : sigmoidoscopy and colonoscopy. Both techniques offer the advantage of immediate polypectomy which combines preventive screening and definite therapy in one step. Numerous studies (Evidence grade II-2) could show that screening colonoscopy combines high rates of sensitivity and specificity with cost-effectiveness. However it must be guaranteed that there are standards concerning the quality of the examination and the technical equipment. Under these conditions, Germany has implemented this procedure into its cancer screening program in 2002. This means screening colonoscopy is now covered by medical insurance. Experiences from the last years show that screening colonoscopy is able to reduce the incidence of the CRC, already existing tumors are diagnosed in an earlier -well treatable- stage, the procedure is cost-effective, and the rate of complications is very low. To date, the most important problem appears to be the very limited acceptance in the wide public – a point that will have to be improved in the future.

- S 05 -

VIRTUAL COLONOSCOPY : THE NEW TOOL FOR SCREENING ! D. Bielen, Leuven, KUL.

Colorectal cancer is even today a major health issue, being third most frequent cancer worldwide ([1]). Fortunately, these tumors develop in 70-90 % of the cases from pre-existing benign polyps over 5-10 years. Early screening for and removal of these polyps is therefore indicated ([2]). For persons at high risk (2- to 4-fold lifetime risk) the American Gastroenterological Association (AGA) recommends just conventional colonoscopy starting at age 40 or 10 years prior to the age of diagnosis in a first-degree relative ([3]). The population, with a lifetime risk of 4-6 %, has a large choice : FOBT (fecal occult blood test), sigmoidoscopy, combination of FOBT and sigmoidoscopy, conventional colonoscopy and double contrast barium enema. Screening should start at age 50. Conventional colonoscopy is accepted being gold standard, although it has no 100 % sensitivity ([4]). Large scale screening for colorectal cancer with conventional colonoscopy can lead to increased workload for gastroenterologists and even waiting lists for patients! This opens

perspectives for virtual colonoscopy as alternative or complementary tool for screening. This CT based technique, developed in the 90's, allows non-invasive visualization of the colonic wall for detection of polyps (5).
The 'Working Group on Virtual Colonoscopy' (Boston, October 2003) advices : bowel prep with Fleet Phosphosoda®), combined with fecal tagging ([6]) ; low dose (≤ 50 mAs) thin slice (≤ 3 mm) multi-slice CT ; retrograde filling of the colon with room air or carbon dioxide ; supine and prone acquisition ([7]).
Virtual colonoscopy can also be used for surveillance after polypectomy or surgery, to detect proximal lesions in case of an obstructing tumor, or when conventional colonoscopy is contra-indicated, incomplete or refused. Advantages are the non-invasiveness, the short examination time and the additional information of the extra colonic structures. Drawbacks are the need for bowel prep, time for interpretation (up to 60 minutes), the use of ionizing radiation and the inability to remove polyps. The problem of the ionizing radiation can be solved by using magnetic resonance colonography, a technique with promising results ([8]). The sensitivity for lesions ≥ 1 cm varies from 94 % in 'good circumstances' ([4]) to just 55 % in 'daily practice circumstances' ([9]).
The emergence of the virtual colonoscopy together with other new detection techniques (DNA mutations in stool, proteins in the blood, …) necessitate for cooperation between gastroenterologists and radiologists! The radiologist should offer diagnostic virtual colonoscopy, whereas the gastroenterologist can offer a-same-day therapeutic conventional colonoscopy in case of a positive virtual colonoscopy, without the necessitation for additional bowel prep. The threshold for referral depends on the size of the 'significant' polyp! For polyps of 6 mm, 70,3 % will not be referred, 86,5 % for 8mm polyp size and up to 92,5 % for 10mm polyp size! How to elaborate this 'joint venture' in time and space is at the moment unclear, but for patient and public health reasons, it is worth paying attention to this opportunity!

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COLORECTAL CANCER SCREENING – THE PUBLIC/PROFESSIONAL INTERFACE. L. Aabakken. Dept of medical gastroenterology Rikshospitalet University Hospital Oslo, Norway.

The burden of colorectal cancer in Europe is severe and increasing. There is political as well as medical impetus in the direction of nationwide screening programs. The sepcifric strategies for screening vary, however, indicating the lack of hard evidence to support the various alternatives. Even more variation is seen in the choice of strategies for implementing the screening program that is chosen for a country. The challenge of motivating the public to adhere to screening programs is daunting, and yet, the success of any screening program relies completely on the ability of the health authorities to recruit the public. To facilitate this aspect of colorectal cancer screening, a joint meeting of the European Society of Gastrointestinal Endoscopy (ESGE) and the Public affairs committee of UEGF was held in Oslo June 2003. This talk reports some of the output from that meeting.

What message to convey ?

This was – not surprisingly, the most debatable subject, and no consensus was reached. At present, there are no randomized trials available to support sigmoidoscopy, although such data are underway. More importantly, similar data on colonoscopy are lacking altogether. Despite the finite amount of published data, the consequences to be drawn varied

widely between countries, from no screening to full support for colonoscopy programs. The discrepancy was due to varying support of the notion "anything is better than nothing". The most adamant opponents to colonoscopy screening held that once such a program is initiated, the option to perform randomized trials to determine the true value of such a program will be politically and practically undoable. However, it was agreed that any screening program is of value only when it is performed according to intentions, including an acceptable public compliance. Thus, the public interface aspects apply regardless the chosen strategy.

Approaching the public

To adequately approach the public with a health message, barriers to dissemination must be identified, and the optimal channels of information and – persuasion – must be determined. *Population* barriers include lack of knowledge of the disease, awareness of risk factors and important symptoms, and embarrassment related to a gut disease. The concept of colonoscopy also scares many screenees. *Provider* barriers relate to unawareness or lack of focus, particularly within primary care. This may in part be due to insufficient knowledge of the utility of e.g. polypectomy but lack of resources may also be involved. The primary care physician must prioritize his time intensely and weigh the issues of CRC screening against numerous other important fields of focus. Thus, awareness activities must address the primary care doctors as well. Finally there are *health care system* barriers – primarily lack of economic and political incentives to promote screening. Inadequate reimbursement arrangement will kill any screening program, regardless of scientific foundation. To access the public directly, the utility of famous persons to promote the issue cannot be overestimated. In several countries, individuals with personal experience with colon cancer have made a tremendous impact by bringing the issue forward in the media limelight. While such an opportunity hardly can be devised by the screening program organizers, it is of major importance to nurture any such initiative should it appear.

Ethical and legal considerations

The responsibilities taken on by a health care system and a doctor that offers screening to healthy persons are wholly different from those related to the regular situation, where the doctor is approach by a patient with a problem he or she needs to solve. This has implications at many levels, e.g. the amount and content of the information given and the quality assurance mechanisms of the facilities that will perform the procedures. False positive and false negative tests will always occur, and the legal as well as the ethical dilemmas relating to that must be clarified before a screening program is launched. Finally, the cost issues of any screening program has ethical implications, since this money at some level will be deducted from other segments of the health care system, given a fixed total sum.

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ECONOMIC IMPACT OF A COLORECTAL CANCER SCREENING PROGRAM IN BELGIUM. M. Buset, President of the Belgian Society of Gastrointestinal Endoscopy, CHU Saint-Pierre, ULB, Brussels.

Colorectal cancer is the second leading cause of cancer death in most developed countries, including Belgium (more than 6000 new cases per year, half of them will die of the disease). It has several features that make it ideal for screening. First, it is both common and serious. Second, it has a readily identifiable and slow growing precursor lesion, the adenoma, removal of which prevents progression to cancer and save lives. The "National Polyp Study" has shown that the clearing of the colon adenomas by polypectomy experienced a 76-90 % reduction in colorectal cancer incidence, with no cancer death ([1]). Third, early detection reveals tumors at stages that are readily curable by surgery (Dukes A or B). Fourth, currently recommended prevention tests are widely available. National cancer screening programs are currently undergoing, not only in the USA, but also throughout Europe, in France, Germany, Italy, the UK, all Scandinavian countries… In Belgium, even if some effort have been undertaken to promote prevention, such as breast cancer and mammogram, or lung cancer and anti-tobacco laws, no national colorectal cancer screening program exists. Even if at present, only annual FOBT the only method which has been proved to significantly decrease the mortality from colorectal cancer in prospective controlled randomized studies ([2]), other options have been proposed by the American AHCPR (Agency for Healthcare Policy and Research), which are flexible sigmoidoscopy every 5 yr with or without annual FOBT, double-contrast barium enema every 5-10 yr or colonoscopy every 10 yr. Other options may also become recommendable in the next future, such as stool DNA detection or CT or MR virtual colonography.

Cost-effectiveness is a matter of primordial importance when mass screening is concerned. At present, only American studies are available. Most of these use the Markov statistical model. They take into account all states of the adenoma-

carcinoma sequence from normal to death, and the influence of screening tests on the probability of moving from on state the next one. All costs are considered in each state, including efficiency, safety, and potential complications of each involved procedure, either diagnostic or therapeutic. In most of these American studies, the most cost-effective screening strategies appear to be either annual FOBT with flexible sigmoidoscopy every 5 yr or colonoscopy every 10 yr.

The sensitivity analysis an these epidemiological and economic data are strongly influenced by several parameters, including specificity of the screening test, most of all by compliance of the screened population, but also by the local costs. Among all, colonoscopy exerts a major economic influence, because it is part of all screening strategies. It is widely accepted that polyp identification and removal constitutes the keystone of an affective prevention of cancer, and colonoscopy is the only method usable to confirm another positive test or to remove a polyp or an early cancer. The mean level of reimbursement of a diagnostic colonoscopy in the US is $695.95 while it is only 143.31 euros in Belgium. Even so, the cost-effectiveness ratio for colorectal cancer screening is estimated to be 1/3d of breast cancer screening, 1/25th of heart transplantation, and 1/38th of cervical cancer screening, in terms of cost/life year gained (not even speaking of airbags in cars or smoke detectors in hotel rooms!). Leshno *et al.* recently published a cost-effectiveness study in the average risk population in Israel ([3]). This country and Belgium are fairly comparable in terms of cancer epidemiology, medical facilities, and most of all for this purpose, in terms of medical costs (the equivalent of 158.41 euros for colonoscopy). This study compares five screening strategies, starting at 50 years of age : no screening, one-time colonoscopy screening, colonoscopy, repeated after 10 years, annual FOBT, annual FOBT and sigmoidoscopy in a 5-year interval. The lifetime cost of the procedure was estimated to 279 euros for a once in a lifetime colonoscopy, 491 euros for a colonoscopy every 10-year and 509 euros for no screening, which means doing nothing but treating the advert cancers. This study clearly demonstrates that screened subjects not only live longer than unscreened ones (a mean of 55 to 66 days), but also cost less, which means colorectal cancer screening saves public money!

These figures can be projected to Belgium. The history of the breast cancer-screening program in Belgium may serve as a preliminary comparison tool. Since the national campaign started in 1986, the number of mammograms increased by 60.150 every year, to reach a coverage rate of 27.3 % in the 50-69 year old age group at present. If a national program of colorectal cancer screening should be implemented now in the population aged from 50 to 69 with a penetration rate similar to that observed for breast cancer screening, 27.3 % of the 2.287.468 of that age cohort should be screened every 10-year, that is to say 624.000 subjects. Considering a progressively rising number of expected screened subjects, it would reach an annual cost of around 13 million euros in 2016. Of course, a 27.3 % compliance rate for colorectal cancer screening may be quite an optimistic prospective. In the US, compliance to colorectal cancer screening is only one third of that to breast cancer. Awareness campaigns, such as the 1999 campaign of the Belgian Society of Gastrointestinal Endoscopy, may at last improve that situation.

Colonoscopy every 10-year is probably the method which should be preferred, as proposed by the American College of Gastroenterology ([4]), because it is the most effective prevention test currently available. It has the highest sensitivity rate, and allows simultaneous polyp diagnosis and removal. Its relatively low cost in our country compared to the US makes it also the most cost-effective screening procedure. But this opinion is of course susceptible to change in the future if new efficient, noninvasive and cost-effective technologies are developed.

Conclusion : For average risk groups, screening of colorectal cancer should start at age 50 yr., and should be available to the whole population, according to personnel choices and adequate information. We need to sustain an unequivocal pressure on our national deciders to implement a nationwide campaign and obtain a full coverage of the cost of screening through our social security system. We need the energy of everyone, from the general practitioner to every scientific society, otherwise Belgium might remain the last country with a high-risk population to keep an intolerable risk of death from colorectal cancer.

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Acknowledgements to Michel Huybtechts for his precious collaboration.

WICH IS THE STRATEGY FOR CANCER SCREENING IN BELGIUM : THE POLITICAL POINT OF VIEW.
C. Fonck. Childhood, Help to Youth and Health Ministery of the French Community.

The prevention is one of the priorities of the Health Ministery of French Community. Now, a breast screening programme exists in our country, by the mammotest. This programm is organized by the Ministery with the collaboration of the “Centres de Coordination Provinciaux (CCP)”. This action concerns the women between 49 and 60 years of age. But, by this programm, only 10 to 15 % of the concerned women are covered. Nevertheless, about a percentage of fifty has a screening with the mammotest and others techniques, mammography, echography.

As it is good known, many others cancers are very frequen, particularly the colorectal cancers. In Belgium more than 6.000 cases ares diagnosed per year, especially among the persons after 50 years. More, some people are really exposed at this risk : familial history of polyps, inflammatory bowel diseases, familial polyposis syndromes…
Colorectal cancer screening is thus a problem of public health.
Primary prevention is also one matter of my Cabinet : healthy diet, alcohol consumption, tobacco, environment agents… Although difficult, this prevention is very important especially for the future.
For the precocious detection, the best method must be defined. The screening requires the application of tests to a large number of people in order to identify those who are likely to have disease. Several questions must have responses :

a) benefits in terms of survival of the patients discovered and treated,
b) high-risk subgroups identified,
c) screening tests with good predictive value available,
d) community health resources adequate,
e) costs of the screening
f) patient compliance,
g) risk of the method.
h) age brackets

The specialists are there to point out the best screening method : FOBT, sigmoïdoscopy, total colonoscopy, virtual colonoscopy by scanner and perhaps bloodtests and stooltests, more specific in the future. It is necessary to have a good defined target and to establish the means to realize the objective.

- S 09 -

HOW TO MANAGE A PATIENT WITH MINIMAL HCV CHRONIC HEPATITIS. S. Zeuzem, Saarland University Hospital, Germany.

The primary goal of treatment for hepatitis C is eradication of the virus. Clinically this is defined as a sustained virologic response, and is evidenced by undetectable hepatitis C virus (HCV) RNA in serum by sensitive molecular tests 24 weeks after completion of treatment. Sustained virologic response rates have increased considerably over the last decade as treatment strategies have evolved from interferon monotherapy to combination IFN plus ribavirin. More recently, the introduction of pegylated IFNs has further improved sustained virologic response rates, such that more than half of patients overall can now expect a successful outcome after treatment with a pegylated interferon in combination with ribavirin. Approximately 25 %-40 % of patients with chronic hepatitis C have ALT activity that is persistently in the normal range. It is generally believed that these patients have milder hepatitis and slower disease progression than patients with elevated ALT activity. Several studies, however, have reported marked liver lesions, including cirrhosis, in patients with persistently normal ALT levels and chronic hepatitis C. Moreover, the evolution and clinical outcome of chronic hepatitis C, and the durability of normal ALT activity in these patients is unknown. Follow-up analyses of up to 10 years in this population have demonstrated that ALT elevations occur in > 20 % of patients. Currently, there is no reliable method to identify patients at risk of progressing to severe liver disease. Patients with persistently normal ALT have been routinely excluded from pivotal treatment trials. Consequently, knowledge of the efficacy of interferon-based therapies is limited in this subgroup. It is important to note that the definition of normal ALT activity, and the concept of persistently normal ALT activity in patients with chronic hepatitis C are arbitrary. New criteria for the range of normal ALT activity have recently been proposed. Controversial efficacy results have been obtained with standard interferon in a few trials that have enrolled a limited number of patients with normal ALT levels. These results together with the reported risk of ALT flares during interferon treatment have led US and European experts to recommend against treatment in this subgroup until data from large multicentre trials becomes available. In the yet largest randomized international multicenter trial, a total of 491 patients with at least 3 normal ALT values over an 18-month period were randomized to treatment with peginterferon alfa-2a 180 mg/week plus ribavirin 800 mg/day for 24 weeks (212 patients), the same combination for 48 weeks (210 patients), or no treatment (69 patients). Treated patients were followed for 24 weeks after completion of therapy. Control patients were monitored for 72 weeks. The primary measure of efficacy was the sustained virologic response (SVR), defined as undetectable serum HCV RNA by qualitative PCR at the end of 24-weeks of untreated follow-up. SVR rates of 30 % and 52 % were obtained in the 24- and 48-week treatment groups, respectively, and 0 % in the untreated control group. In patients infected with HCV genotype 1, SVR rates of 13 % and 40 % were obtained with 24 and 48 weeks of treatment, respectively ($p < 0.0001$). In patients infected with genotypes 2 or 3, SVR rates were 72 % and 78 %, respectively ($p = 0.452$). Remarkably, 52 % of the patients in the untreated control group experienced ALT elevations above the ULN during the study. This incidence is higher than previously reported, and supports the concept that, in many patients, the persistence of the ALT activity within normal levels is a function of monitoring frequency. Furthermore, ALT increases are unpredictable and may reflect the risk of progression of liver disease. This suggests that ALT activity may be an unreliable guide for treatment decisions. Indeed, treatment of patients with chronic hepatitis C should rely on the probability of viral eradication, symptoms, histology, anticipated progression of disease, and the risk of transmission (e.g. health care workers) rather than on a single biochemical parameter.

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MINIMAL CHRONIC HCV HEPATITIS : THE CONTRA APPROACH REGARDING THE PLACE OF ANTIVIRAL THERAPY. Y. Horsmans. Department of Gastroenterology. Cliniques Universitaires St-Luc (UCL).

Until now, international guidelines have strongly discouraged the treatment of chronic hepatitis (HCV) patients with persistently normal alanine aminotransferase (ALT) levels and/or minimal hepatitis on histology. Taking into account these guidelines, it is very easy to sustain the following point-of-view: abstention to treat these patients (without any sign of other viral co-infection) should and must be the rule. One exception should however been mentioned : patients with persistently normal ALT levels and advanced liver fibrosis. Such a situation is encountered in around 20 % of individuals with persistently normal ALT values ([1]). This exception, i.e. rare cases of patients with persistently normal ALT levels and advanced fibrosis, must be kept in mind and should be distinguished from patients with minimal hepatitis.
Looking at the recent literature, progress has been made regarding our knowledge about antiviral therapy in patients with normal ALT level and/or minimal hepatitis: it has been demonstrated that these patients benefit from antiviral therapy to the same extent than patients with abnormal ALT values and/or more advanced liver histology scores ([2-5]). Similarly, occurrence of side effects seem to be identical in all groups of patients.
Finally and potentially more interesting, data is accumulating showing that HCV patients with an initial picture of F0 or F1 fibrosis are less likely to develop progression of fibrosis ([6, 7]).
In the debate on the place of antiviral therapy in patients with minimal hepatitis, the decision to initiate treatment should be based on a combination of factors independent of ALT levels including amount of fibrosis on histology, HCV genotype and viral load, patient age and motivation, co-morbid illness, and the presence of other complicating conditions as stated by Strader et al ([8]). The presence of minimal hepatitis alone as a single criteria thus remains a very strong argument against the initiation of antiviral treatment.

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XVIIth Belgian Week of Gastroenterology
February 24-26, 2005
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ABSTRACTS

A01 — A34	Belgian Association for the Study of the Liver (BASL)
B01 — B16	Research Group "Gastrointestinal Regulatory Mechanisms (OG-NFWO)"
C01 — C08	Belgian Helicobacter Pylori Study Group
	Belgian Group of Digestive Oncology
D01 — D74	Joint Meeting of Gastroenterology
L01 — L08	Immunology IBD Meeting
P01 — P15	Gastro-intestinal Pathology Club
R01 — R09	Research Group "Digestive and Abdominal Imaging"
T01 — T05	Belgian Pancreatic Club
V01	Belgian Videocapsule Group
X01 — X06	Research Group of Clinical Nutrition and Metabolism (SBNC and VVKVM)
	Belgian Group of Pediatric Gastroenterology and Nutrition
S01 — S10	Symposium of the six societies "UNRESOLVED ISSUES IN GASTROENTEROLOGY"

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AERSSENS J.	B03, B05	
AERTS R.	D44, D63, D67, P14	
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ALAERTS H.	P12	
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DE LOOZE D.	D29	Moderator Joint Meeting D14-D21
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DE MAEYER M.	X02	
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