NEDERLANDSE VERENIGING VOOR GASTROENTEROLOGIE

Sectie Gastrointestinale Endoscopie

Netherlands Society for Parenteral and Enteral Nutrition

Sectie Neurogastroenterologie en Motiliteit

Sectie Experimentele Gastroenterologie

Sectie Kindergastroenterologie

Sectie Endoscopie Verpleegkundigen en Assistenten

Vereniging Maag Darm Lever Verpleegkundigen

★

NEDERLANDSE VERENIGING VOOR HEPATOLOGIE

★

NEDERLANDSE VERENIGING VOOR GASTROINTESTINALE CHIRURGIE

★

NEDERLANDS GENOOTSCHAP VAN MAAG-DARM-LEVERARTSEN

★

NH KONINGSHOF

VELDHOVEN

INHOUDSOPGAVE **pag.**

Tijdstippen ledenvergaderingen:

Assistentenvereniging Touché (mdl-artsen i.o.)	17 maart, 12.15 uur - Zaal 82/83
Nederlandse Vereniging voor Hepatologie	17 maart, 15.00 uur - Parkzaal
Nederlandse Vereniging voor Gastroenterologie:	17 maart, 21.30 uur - Brabantzaal
Nederlandse Vereniging voor MDL-Verpleegkundigen	18 maart, 10.05 uur - Auditorium
Nederlands Genootschap van Maag-Darm-Leverartsen	18 maart, 12.00 uur - Zaal 82/83
Sectie Endodoscopie Verpleegkundigen en Assistenten	18 maart, 12.00 uur - Diezezaal

VOORWOORD

Hierbij treft u het volledige programma aan van de komende voorjaarsvergadering te Veldhoven.
Het programma zal van start gaan om 13.00 uur.

De Nederlandse Vereniging voor Hepatologie start iets eerder om 12.30 uur met vrije voordrachten en vervolgt na de theepauze met het symposium 'Leverupdate ter ere van levericonen: Van Berge Henegouwen en Schalm'.

Op donderdagmiddag heeft de NVGIC naast vrije voordrachten, een symposium, getiteld: 'Screening voor het colorectale carcinoom'. Vrije voordrachten zijn er verder van de Nederlandse Vereniging voor Gastroenterologie, de Sectie Neurogastroenterologie en Motiliteit en NESPEN.

Tijdens de plenaire avondsessie, die om 20.00 uur van start gaat met de Presidential Selection, zal om 21.00 uur de Altana lecture plaatsvinden ditmaal verzorgd door Prof. R.J. Nicholls. De voordracht is getiteld: Restorative Proctocolectomy in 2005'. Alle leden worden van harte uitgenodigd deze avond aanwezig te zijn!

Op vrijdag zijn er sessies met vrije voordrachten van de Sectie Gastrointestinale Endoscopie, de Nederlandse Vereniging voor Gastroenterologie en de Sectie Experimentele Gastroenterologie. Tijdens de International Teaching Session spreekt Prof. dr. J. Prieto over "The promise of gene therapy in hepato-gastrointestinal disorders". Voorts zijn er symposia over chronische pancreatitis en colonkankerscreening en wordt er aandacht besteed aan de richtlijn oesophaguscarcinoom.

In de Diezezaal en het Auditorium worden tenslotte eigen programma's verzorgd door Sectie Endoscopie Verpleegkundigen en Assistenten en de Vereniging van Maag Darm Lever Verpleegkundigen.

Tenslotte nog een aandachtspunt voor de sprekers: u dient zich strikt te houden aan de beschikbare spreektijd! U vindt dit aangegeven bij de betreffende sessie. Indien u een eigen laptop gebruikt, dan dient u deze aan te sluiten tijdens de discussietijd van de spreker voor u. In **zaal 25** kunt u uw Power Point presentatie tevoren controleren.

Graag tot ziens in Veldhoven!

Dr. E.C. Klinkenberg-Knol, secretaris
Nederlandse Vereniging voor Gastroenterologie

N.B. De met een asterisk gemerkte abstracts in het programma zijn ingezonden door leden van de Sectie Kindergastroenterologie.

Programma donderdag 17 maart 2005

DONDERDAG	BRABANTZAAL	BARONIEZAAL	PARKZAAL	AUDITORIUM	DIEZEZAAL
12.30			Vrije voordrachten Nederlandse Vereniging voor Hepatologie p. 13	Op donderdag geen programma in deze zaal.	Op donderdag geen programma in deze zaal.
13.00	Vrije voordrachten Nederlandse vereniging voor Gastrointestinale Chirurgie p. 7	Vrije voordrachten Sectie Neurogastroenterologie en Motiliteit en NESPEN p. 10	Vervolg vrije voordrachten Nederlandse Vereniging voor Hepatologie p. 13		
15.00	Theepauze	Theepauze	Theepauze/vergadering NVH		
15.30	**Mini-symposium**: '**Screening voor het colorectale carcinoom'** p. 8	Vrije voordrachten NVGE en Sectie Neurogastroenterologie en motiliteit p. 11	**Symposium**: **'Lever-update ter ere van lever-iconen: Van Berge Henegouwen en Schalm'** p. 14		
17.00	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie p. 9	Vervolg vrije voordrachten NVGE en Sectie Neurogastroenterologie en motiliteit	Vervolg symposium NVH		
17.30	Congresborrel / diner	Congresborrel / diner	Congresborrel / diner		
20.00 – 21.30	**Presidential Selection gevolgd door Altana Lecture verzorgd door R.J. Nicholls** p. 15				
21.30 – 22.00	Ledenvergadering NVGE				

Programma vrijdag 18 maart 2005

VRIJDAG	BRABANTZAAL	BARONIEZAAL	PARKZAAL	AUDITORIUM	DIEZEZAAL
08.30	Casuïstiek voor de klinikus, vrije voordrachten Sectie Gastrointestinale Endoscopie p. 16	**Richtlijn oesophaguscarcinoom** p.17	Vrije voordrachten Sectie Experimentele Gastroenterologie p.19	09.30 Ontvangst leden Vereniging voor Maag Darm Lever Verpleegkundigen p. 25	
10.00	koffiepauze	Koffiepauze	Koffiepauze	Aanvang sessie VMDLV	
10.30	**Mini-symposium 'Chronische pancreatitis: Facts and fiction'** p. 17	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie p. 18	Vervolg Vrije voordrachten Sectie Experimentele Gastroenterologie p. 20	Vervolg programma VMDLV	Ontvangst Sectie Endoscopie Verpleegkundigen en Assistenten p. 26
11.00	Vervolg symposium	Vervolg vrije voordrachten Nederlandse Vereniging voor Gastroenterologie	**International Teaching Session** spreker: Prof. dr. J. Prieto p. 21	Koffiepauze, vervolgprogramma VMDLV: 11.15 uur	Aanvang sessie SEVA
12.00	Lunchbuffet in expositiehal	Lunchbuffet in expositiehal	Lunchbuffet in expositiehal	Lunchbuffet in expositiehal	Lunchbuffet in expositiehal
13.30	**Symposium 'Colonkankerscreening'** p. 21	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie p. 21	Vrije voordrachten Sectie Experimentele Gastroenterologie p. 23	Vervolg programma Vereniging Maag Darm Lever Verpleegkundigen	Vervolg programma met om 14.30 uur ledenvergadering SEVA
15.00	Theepauze/einde van alle programma's	Theepauze/einde van alle programma's	Theepauze/einde van alle programma's	Theepauze/einde van alle programma's	Theepauze/einde van alle programma's

CURSORISCH ONDERWIJS IN MAAG-DARM-LEVERZIEKTEN **AUDITORIUM**

Cursuscommissie:	Prof. Dr. C.J.J. Mulder (voorzitter) (MDL, VUMC) Dr. H.M. van Dullemen (MDL, AZG) Dr. C.M.F. Kneepkens (KA, VUMC) Dr. C.J.H.M. van Laarhoven (chirurg, Elisabeth Tilburg) Dr. M.E. van Leerdam (MDL i.o., Erasmus MC) R. Quispel (MDL i.o., UMCU) Dr. B.P.L. Wijnhoven (AGIO Heelkunde, Erasmus MC)

Woensdag 16 maart 2005

20.30 - 21.00 uur	IBD bij kinderen *Dr. J.C. Escher, MDL, EMC*
21.00 - 21.30 uur	IBD bij volwassenen, gediagnosticeerd op jonge leeftijd *Dr. C.J. van der Woude, MDL, EMC*
21.30 – 22.00 uur	Obstipatie bij kinderen *Dr. M.A. Benninga, MDL, AMC*
22.00 - 22.30 uur	Obstipatie bij volwassenen, gediagnosticeerd op jonge leeftijd *Dr. G.E.E. Boeckxstaens, MDL, AMC*

Donderdag 17 maart 2005

08.00 – 08.30 uur	Chirurgische behandeling van anusatresie; Nijmeegse ervaring *Dr. P.N.M.A. Rieu, Kinderchirurgie, UMCN*
08.30 – 09.00 uur	Chirurgische (thorascopische) behandeling van oesophagus atresie; Utrechtse ervaring *Prof. dr. N.M.A. Bax, Kinderchirurgie, UMCU*
09.00 – 09.40 uur	Gastric pull-up for long-gap oesophageal atresia *Prof. dr. L. Spitz, Great Ormondstreet Children's Hospital*
09.40 – 10.10 uur	Kwaliteit van leven als volwassene na slokdarmatresie *Drs. J.A. Deurloo, Kinderchirurgie, AMC*
10.10 – 10.40 uur	koffiepauze
10.40 – 11.10 uur	Levertransplantatie voor galgangatresie. Hoe worden ze volwassen? *Prof. dr. M.J.A. Slooff, Heelkunde, UMCG*
11.10 - 11.40 uur	Mucoviscoidose op de kinderleeftijd *Dr. H.J. Verkade, Kindergeneeskunde, UMCG*
11.40 - 12.10 uur	Good care for people with CF *Prof. J.M. Littlewood, St. James Hospital, Leeds*

De cursuscommissie verwacht van de MDL-artsen i.o. dat ze de Cursus Klinische Hepatologie (NVH) éénmaal bezoeken in de eerste drie jaar van de opleiding en minimaal één maal in het tweede deel van de MDL-opleiding.

Nederlandse Vereniging voor Gastrointestinale Chirurgie **Brabantzaal**

12.30 Inschrijving, koffie

Voorzitters: C.J.H.M. van Laarhoven en L.P.L. Stassen

Voordrachten in het Nederlands, spreektijd 7 minuten, discussietijd 3 minuten.

13.00 A prospective analysis of patients with adenocarcinoma of the gastric cardia and lymph node metastasis in the proximal field of the chest *(p. 27)*
S.M. Lagarde[1], H.A. Cense[1], J.B.F. Hulscher[1], H.W. Tilanus[2], F.J.W. Ten Kate[3], H. Obertop[1], J.J.B. van Lanschot[1]. Depts of Surgery[1] and Pathology [3], Academic Medical Centre at the University of Amsterdam and Dept of Surgery[2], Erasmus Medical Centre Rotterdam, The Netherlands

13.10 Additional Value of Positron Emission Tomography in Preoperative Staging of Esophageal Cancer: a Prospective Cohort Study *(p. 28)*
M. Westerterp[1], H.L. van Westreenen[2], G.W. Sloof[3], P.L. Jager[4], O.S. Hoekstra[5], E.F.I. Comans[5], H. Groen[6], P.M.M. Bossuyt[7], J. Stoker[8], H.M. van Dullemen[9], P. Fockens[10], E.J. van der Jagt[11], J.J.B. van Lanschot[1], J.Th.M. Plukker[2]. Depts of Surgery[1], Clinical Epidemiology and Biostatistics[7] , Nuclear Medicine[3], Gastroenterology[10] and Radiology[8], Academic Medical Center, Amsterdam, Dept of Nuclear Medicine[5], VU University Medical Center, Amsterdam, Depts of Surgery[2] and Nuclear Medicine/PET-center[4], Office for Medical Technology Assessment[6] and Dept of Gastroenterology[9] and Radiology[11], Groningen University Medical Center, The Netherlands

13.20 Extracapsular lymph node involvement in patients with adenocarcinoma of the distal esophagus and gastroesophageal junction *(p. 29)*
S.M. Lagarde[1], D. de Boer[1], F.J.W. Ten Kate[2], O.R.C. Busch[1], H. Obertop[1], J.J.B. van Lanschot[1]. Depts of Sugery[1] and Pathology[2], Academic Medical Centre at the University of Amsterdam, The Netherlands

13.30 Minimally invasive approach in acute necrotising pancreatitis: a strategy for a selected subgroup or a potential benefit for all? Dutch Acute Pancreatitis Study Group. *(p. 30)*
M.G.H. Besselink[1], H.C. van Santvoort[1], T.L. Bollen[2], M.S. van Leeuwen[1], J.S. Lameris[3], S.P. Strijk[4], Van der Jagt[5], H.S. Hofker[5], C.H. Dejong[6], Boermeester[3], Van Ramshorst[2], A.F.M. Schaapherder[7], C.J.H. van Eijck[8], J.P.E.N. Pierie[9], M.A. Cuesta[10], J.F. Lange[11], H. van Goor[4], H.G. Gooszen[1] for the Dutch Acute Pancreatitis Study Group. Depts of Surgery and Radiology: University Medical Center Utrecht[1], St. Antonius Hospital Nieuwegein[2], Academic Medical Center Amsterdam[3], University Medical Center St.Radboud[4], University Hospital Groningen[5], University Hospital Maastricht[6], Leiden University Medical Center[7], Erasmus Medical Center Rotterdam[8], Medical Center Leeuwarden[9], Free University Medical Center Amsterdam[10], Medical Center Rijnmond Zuid, Rotterdam[11], The Netherlands

13.40 Risk Adjusted Prediction of Operative Morbidity in Patients undergoing Pancreato-duodenectomy with the use of POSSUM *(p. 31)*
S.M.M. de Castro, J.T. Houwert, K.F.D. Kuhlmann, O.R.C. Busch, T.M. van Gulik, H, Obertop, D.J. Gouma. Dept of Surgery, Academic Medical Center, Amsterdam, The Netherlands

13.50 Prophylactic probiotics reduce bacterial translocation in experimental pancreatitis *(p. 32*)
F. Lutgendorff, L.P. van Minnen, H.M. Timmerman, H.G. Gooszen, L.M.A. Akkermans. Gastrointestinal Research Unit, Depts of Gastroenterology and Surgery, University Medical Center Utrecht, The Netherlands

14.00 Synergistic effect of interstitial laser coagulation and doxorubicin in a murine model for solitary colorectal liver metastasis. *(p. 33*)
L.M. Veenendaal, R. van Hillegersberg, N. Smakman, J.D.W. van der Bilt, O. Kranenburg, I.H.M. Borel Rinkes. Dept of Surgery, University Medical Center Utrecht, The Netherlands

14.10 Ischemia/reperfusion accelerates the outgrowth of hepatic micrometastases in a highly standardized murine model. *(p. 34*)
J.D.W. van der Bilt[1], E.A. te Velde[1], M.W. Nijkamp[1], N. Smakman[1], L.M. Veenendaal[1], E.E. Voest[2], P.J. van Diest[3], O. Kranenburg[1], R. van Hillegersberg[1] and I.H.M. Borel Rinkes[1]. Dept of Surgery[1], Medical Oncology[2] and Pathology[3], University Medical Center Utrecht, The Netherlands

14.20 First experiences with the use of Imatinib in gastro-intestinal stromal tumours. *(p. 35*)
M.F. Ernst[1], S. Rodenhuis[2], F. van Coevorden[1]. Dept of Surgical[1] and Medical[2] Oncology The Netherlands Cancer Institute / Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands

14.30 A clinical prediction model to select patients with secondary peritonitis for relaparotomy *(p. 36*)
B. Lamme[1], O. van Ruler[1], D.J. Gouma[1], J.B. Reitsma[2], M.A. Boermeester[1]. Dept of Surgery[1] and Dept of Epidemiology and Biostatistics[2], Academic Medical Center Amsterdam, The Netherlands

14.40 Long-term outcome in terms of Quality of life (QOL), small bowel obstruction, body image and cosmesis after hand-assisted laparoscopic (HAL) vs open proctocolectomy with ileal pouch-anal anastomosis (IPAA): a randomised trial. *(p. 37*)
S.W. Polle[1], M.S. Dunker[1], J.F.M. Slors[1], D.J. Gouma[1], D.W. Hommes[2] and W.A. Bemelman[1]. Depts of Surgery[1] and Gastroenterology[2], Academic Medical Center Amsterdam, The Netherlands

14.50 Excellent results with The Self Expanding Metal Stent as a bridge to surgery *(p. 38)*
R.J.I. Bosker[1], E.H. Eddes[1], F. ter Borg[2], M. Ledeboer[2], M.M.J.J.R. Jaspers[3], M. Eeftinck Schattenkerk[1]. Depts of Surgery[1], Gastroenterology[2] and Radiology[3], Deventer Hospital, The Netherlands

15.00 Theepauze

Nederlandse Vereniging voor Gastrointestinale Chirurgie **Brabantzaal**

MINISYMPOSIUM *"Screening voor het colorectale carcinoom"*

Voorzitters: E.H. Eddes en J.A. Roukema

15.30 First things first.
Dr. J.W.W. Coebergh, epidemioloog, Erasmus MC Rotterdam, afdeling Maatschappelijke Gezondheidszorg en als Hoofd Onderzoek bij Integraal Kankercentrum Zuid

15.45 Bevolkingsscreening op het colorectale carcinoom met 'Fecal Occult Blood Test'
Dr. F. Nagengast, maag-darm-leverarts, UMC St Radboud, Nijmegen

16.00 Endoscopie voor de screening op coloncarcinoom: effectief, maar wie gaat het doen?
Dr. P.D. Siersema, maag-darm-leverarts, Erasmus MC Rotterdam

16.15 Screening en de gevolgen voor de patholoog
Prof. dr. J.H.J.M. van Krieken, patholoog–anatoom, UMC St Radboud Nijmegen

16.30 Centrale discussie van 30 minuten, met voorbereide vragen

17.00 Einde programma

Nederlandse Vereniging voor Gastroenterologie **Brabantzaal**

Voorzitters: M. Sinaasappel en S.D.J. van der Werf.

Voordrachten in het Nederlands, spreektijd 7 minuten, discussietijd 3 minuten.

17.00 Identification of the signal transduction mechanism mediating the anti-inflammatory effect of vagal nerve stimulation *(p. 39)*
E.P.M. van der Zanden[1], W.J. de Jonge[1], G.E. Boeckxstaens[1,2]. Motility center[1] and Dept of Gastroenterology[2], Academic Medical Center, Amsterdam, The Netherlands

17.10 Gastric cancers in young and old patients have different genomic profiles *(p. 40)*
T.E. Buffart[1], B. Carvalho[1], E. Hopmans[1], V. Brehm[2], E. Klein Kranenbarg[2], B.M. Visser[1], B. Ylstra[3], C.J.H. van de Velde[2], G.A. Meijer[1]. Dept of Pathology[1] and Microarray Core Facility[3], VU University Medical Center, Amsterdam and Dept of Surgery[2], Leiden University Medical Center, The Netherlands

17.20 Polyethylene glycol (PEG) as a marker for gastrointestinal permeability: a novel assay, excretion kinetics, and sensitivity *(p. 41)*
A.P.M. Kerckhoffs[1], M.B.M. de Smet[2], M.G.H. Besselink[2], W. Renooij[2], L.M.A. Akkermans[2]. Dept of Gastroenterology[1] and Surgery[2], University Medical Center Utrecht, The Netherlands

17.30 The role of TRAIL-mediated apoptosis in the development of colorectal cancer and possibilities for treatment and prevention (Final report Maag Lever Darm Stichting project WS 01-31) *(p. 42)*
J.J. Koornstra[1], M. Jalving[1], F.E.M. Rijcken[1], S. de Jong[2], H. Hollema[3], E.G.E. de Vries[2], J.H. Kleibeuker[1]. Depts of Gastroenterology and Hepatology[1], Medical Oncology[2] and Pathology[3], University Hospital Groningen, The Netherlands

17.40 Congresborrel in expositiehal

18.00 Diner in de Genderhal

Sectie Neurogastroenterologie en Motiliteit en NESPEN **Baroniezaal**

Chairmen: C.H.C. Dejong / A.A.M. Masclee

Voordrachten in het Nederlands, spreektijd 7 minuten, discussietijd 3 minuten.

13.00 High-fat nutrition inhibits inflammation via the vagus nerve; a novel neuro-immunological pathway. *(p. 43*)
M.D.P. Luyer[1], W.A. Buurman[1], M. Hadfoune[1], J.A. Jacobs[2], C.H.C. Dejong[1], J.W.M. Greve[1]. Dept of Surgery[1], University Hospital Maastricht, The Netherlands

13.10 Intestinal handling during surgery induces an inflammatory response in patients. *(p. 44*)
F.O. The[1], R.J. Bennink[2], W.J. de Jonge[1], D.J. Gouma[3], M.P.M. Burger[4], G.E. Boeckxstaens[1]. Depts of Gastroenterology and Hepatology[1], Nucleair Medicine[2], Surgery[3] and Gynaecology[4], Academic Medical Center Amsterdam, The Netherlands

13.20 Delayed visceral hypersensitivity in maternal separation depends on mast cell degranulation and is mediated by NGF and the nociceptor TRPV-1 *(p. 45*)
R. van den Wijngaard, O. Welting, D. van der Coelen, W. de Jonge en G. Boeckxstaens. Dept of Gastroenterology, Academic Medical Center Amsterdam.

13.30 The vagal anti-inflammatory pathway prevents postoperative ileus by nicotinic acetylcholine receptor activation on intestinal macrophages *(p. 46*)
W.J. de Jonge, E.P. van der Zanden, F.O. The, G.E. Boeckxstaens. Depts of Gastroenterology and Hepatology, Academic Medical Center Amsterdam.

13.40 Vitamin A equivalency of β-carotene in oil in healthy Dutch adults measured using specifically 13C-labelled β-carotene and retinol *(p. 47*)
C.A. Bouwman[1], C.E. West[1,2], R.B. van Breemen[3], D. Zhu[3], M. van Lieshout[4], E. Siebelink[2], P. Versloot[2] and T.H.J. Naber[1]. Dept of Gastroenterology[1], Radboud University Nijmegen Medical Centre and Dept of Human Nutrition[2], Wageningen University, The Netherlands, Dept of Medicinal Chemistry and Pharmacognosy[3], University of Illinois at Chicago, USA and Dept of Nutrition[4], North-West University, South Africa

13.50 Interorgan amino acid exchange across the intestines and the liver in surgical patients *(p. 48*)
M.C.G. van de Poll[1], M.P.C. Siroen[2], P.A.M. van Leeuwen[2], R.G.H. Beets[3], S.W.M. Olde Damink[1], G.C. Melis[2], P.G. Boelens[2], N.E.P. Deutz[1], P.B. Soeters[1], C.H.C. Dejong[1], Depts of Surgery[1] and Radiology[3], Maastricht University and Dept of Surgery[2], VU University Medical Center Amsterdam, The Netherlands

14.00 Continuous L-arginine infusion does not deteriorate the haemodynamic condition in patients with severe sepsis *(p. 49*)
Y.C. Luiking[1], M. Poeze[1], M. Hendrikx[2], P. Breedveld[1], C.H.C. Dejong[1], P.W. de Feiter[1], F. Rubulotta[2], G. Ramsay[2], N.E.P. Deutz[1]. Depts of Surgery[1] and Intensive Care[2], Maastricht University Hospital, The Netherlands.

14.10 Functional Non-Retentive Faecal Soiling in children: 12 years of longitudinal follow-up* *(p. 50*)
W.P. Voskuijl[1], J.B. Reitsma[2], R. van Ginkel[1], J.A.J.M. Taminiau[1], H.A. Büller[3], M.A. Benninga[1]. Dept of Paediatric Gastroenterology and Nutrition[1], Emma Children's Hospital, Dept of clinical epidemiology and biostatistics[2], Academic Medical Centre, Amsterdam, Dept of Paediatrics[3], Sophia Children's Hospital, Rotterdam, The Netherlands

14.20 Threonine incorporation into mucin 2 isolated from intestinal outflow fluid in neonates *(p. 51)* M.W. Schaart, A.C.J.M de Bruijn, H. Schierbeek, I.B. Renes, J.B. van Goudoever. ErasmusMC/Sophia Children's Hospital, Rotterdam, The Netherlands

14.30 Comparison of Magnetic Resonance Imaging and ^{13}C acetic-acid breath test for the assessment of gastric emptying. *(p. 52)*
J.J.L. Haans[1], C.Y. Wong[1], J. Doornbos[2], A. de Roos[2], A.A.M. Masclee[1]. Dept of Gastroenterology & Hepatology[1] and Dept of Radiology[2], Leiden University Medical Center, The Netherlands

14.40 Regional Differences in Expression of SERT and TPH-1 in Patients with Gastroparesis and Healthy Controls (*p. 53)*
N. van Lelyveld, J. ter Linde, M. Samsom. University Medical Centre Utrecht, The Netherlands

14.50 Comparison of sensory perception and reproducibility of electrical mucosal stimulation (EMS) and rapid balloon distension (RBD) of the healthy human rectum *(p. 54)*
M.L. Harris[1], A. Hobson[1], S. Hamdy[1], D.G. Thompson[1], L.M.A. Akkermans[2], Q. Aziz[1]. Section of Gastrointestinal Science[1], University of Manchester, Hope Hospital, Manchester, UK and Gastrointestinal Research Unit, Dept of Surgery[2], University Medical Center Utrecht, The Netherlands

15.00 Theepauze

Ned. Ver. voor Gastroenterologie en Sectie Neurogastroenterologie en Motiliteit **Baroniezaal**

Voorzitters: D.J. de Jong en A.A.M. Masclee

Voordrachten in het Nederlands, spreektijd 7 minuten, discussietijd 3 minuten.

15.30 Octreotide as potential treatment for patientswith non-constipated irritable bowel syndrome *(p. 55)*
T.K. Klooker, H. Beaumont, S.D. Kuiken, A. Lei, G.E. Boeckxstaens. Dept of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, The Netherlands

15.40 Gastric hypersensitivity induced by esophageal acid infusion in healthy volunteers*(p 56)*
B.D. van den Elzen[1], G.N. Tytgat[1], G.E. Boeckxstaens[1]. Dept of Gastroenterology[1], Academic Medical Center Amsterdam, The Netherlands

15.50 Molecular typing methods show different fingerprints for the faecal bacterial composition in irritable bowel syndrome (IBS) patients and healthy subjects. *(p. 57)*
A.P.M. Kerckhoffs[1], M. Samsom[1], G.P. van Berge Henegouwen[1], A.J.P.M. Smout[1], M. van der Rest[2], J. Knol[3], E.A.F. van Tol[3], L.M.A. Akkermans[1]. Depts of Gastroenterology and Surgery[1], Gastrointestinal Research Unit, University Medical Center Utrecht, Microscreen[2], Groningen and Numico Research BV[3], Wageningen, The Netherlands.

16.00 Adults with corrected oesophageal atresia (OA): Are complaints predictive of oesophageal function and/or quality of life (QoL)? * *(p. 58)*
J.A. Deurloo[1], E.C. Klinkenberg[2], S. Ekkelkamp[1], H.A. Heij[1], D.C. Aronson[1]. Pediatric Surgical Center[1], Amsterdam (Emma Children's Hospital/AMC and Vrije Universiteit Medical Center), Dept of Gastroenterology[2], VU University Medical Center, Amsterdam, The Netherlands.

Donderdag 17 maart 2005

Voorzitters: A.A. van Bodegraven en D.J. de Jong

16.10 Early events in antigen-specific CD25neg TR cell induction via the mucosa.(Final report Maag Lever Darm Stichting project no. MWO 02-68) *(p. 59)*
F. Hauet-Broere, L. van Berkel, W. Unger, G. Kraal, J. Samsom. Dept of Molecular Cell Biology and Immunology, VU University Medical Center, Amsterdam, The Netherlands

16.20 Genotypic and phenotypic differences between pediatric/adolescent-onset and adult-onset IBD *. *(p. 60)*
L. de Ridder[1], P.C.F. Stokkers[2], I. Pronk[3], M.A. Benninga[1], J.A.J.M. Taminiau[1], D.W. Hommes[2]. Dept of Pediatric Gastroenterology[1], Emma Children's Hospital, Academic Medical Center, Amsterdam, Dept of Gastroenterology[2] and Lab of Exerimental Internal Medicine[3], Academic Medical Center, Amsterdam, The Netherlands

16.30 The Toll-like receptor 4 (TLR4) Asp299Gly polymorphism isassociated with colonic localization of Crohn's disease, without a major rolefor the Saccharomyces cerevisiae mannan-LBP-CD14-TLR4 pathway *(p. 61)*
R. Mallant-Hent, S. Ouburg, J.B.A. Crusius, A.A. van Bodegraven, C.J.J. Mulder, R. Linskens, A.S. Peña, S.A. Morré. Lab of Immunogenetics and Dept of Gastro-enterology, VU University Medical Center, Amsterdam, The Netherlands

16.40 PCR results of Saccaromyces cerevisiae in intestinal mucosal samples of patients with IBD. *(p. 62)*
R.C. Mallant-Hent[1], M. Mooij[2], R.K. Linskens[4], B.M.E. von Blomberg[3], A.A. van Bodegraven[1], P.H.M. Savelkoul[2]. Dept of Gastroenterology[1] and Medical Microbiology, VU University Medical Centre, Amsterdam, Dept of Gastroenterology, St.Anna Hospital, Geldrop, The Netherlands

16.50 Maintenance treatment with 6-thioguanine in azathioprine or 6-mercaptopurine intolerant inflammatory bowel disease patients *(p. 63)*
N.K.H. de Boer[1], L.J.J. Derijks[2], L.P.L. Gilissen [3], D.W. Hommes [4], L.G.J.B. Engels[5], S.Y. de Boer[6], G. den Hartog[6], P.M. Hooymans[7], A. Makelburg[8], A.H.J. Naber[9], B.D. Westerveld[8], C.J.J. Mulder[1], D.J. de Jong[9]. Depts of Gastroenterology & Hepatology: VU University Medical Centre Amsterdam[1], Academic Hospital Maastricht[3], Academic Medical Center Amsterdam[4], Maasland Hospital Sittard[5], Rijnstate Hospital Arnhem[6], Isala Clinics Zwolle[8], Radboud University Nijmegen Medical Centre[9] and Depts of Clinical Pharmacy: Maxima Medical Centre Veldhoven[2] and Maasland Hospital Sittard[7], The Netherlands

17.00 Long-term results of intravenous cyclosporine in steroid-resistant ulcerative colitis *(p. 64)*
A.B.U. Mäkelburg[1], F.G.A. Jansman[2], J. Vecht[1], B.D. Westerveld[1]. Depts of Gastroenterology[1] and Clinical Pharmacology[2], Isala klinieken, Zwolle, The Netherlands

17.10 Autologous Hematopoietic Stem Cell Transplantation for Severe Refractory Crohn`s Disease *(p. 65)*
Z. Zelinkova[1], M-J. Kersten[3], I. Pronk[1], K. Horsthuis[4], R. van Oers[3], S. Lange[2], D. Hommes[2]. Lab of Experimental Internal Medicine[1] and Depts of Gastroenterology[2], Clinical Hematology[3] and Radiology[4], Academic Medical Centre, Amsterdam, The Netherlands

17.20 FDG-PET detects clinical relevant adenomas of the colon: a prospective study of 100 patients *(p. 66)*
M.C.A. van Kouwen[1], F.M. Nagengast[1], J.B.M.J. Jansen[1], W.J.G. Oyen[2], J.P.H. Drenth[1]. Depts of Gastroenterology and Hepatology[1] and Nuclear Medicine[2], Radboud University Nijmegen, Medical Centre, The Netherlands.

17.30 Heterozygous polymorphisms in the genes encoding ITPA and TPMT*3A are not predictive for the development of adverse effects of Azathioprine treatment in IBD patients* *(p. 67)*
J.M. van Dieren[1], A.J. van Vuuren[1], E.J. Kuipers[1], J.G. Kusters[1], E.E. Nieuwenhuis[2], C.J. van der Woude[1]. Depts of Gastroenterology & Hepatology[1] and Pediatric Gastroenterology[2] Erasmus MC, University Medical Center Rotterdam, The Netherlands

17.40 Congresborrel en aansluitend diner in de Genderhal

Nederlandse Vereniging voor Hepatologie **Parkzaal**

Chairmen: B. van Hoek en L.W.J. Klomp

Voordrachten in het Engels spreektijd 10 minuten, discussietijd 5 minuten.

12.30 The severity of steatosis effects liver regeneration in a rat model *(p. 68)*
R. Vetelaïnen, A.K. van Vliet, T.M. van Gulik. Dept of Surgery (Surgical laboratory), Academic Medical Center Amsterdam,The Netherlands

12.45 Direct and synergistic inhibition of hepatitis C virus replication by cyclosporin a and myocophenolic acid *(p. 69)*
L.J.W. van der Laan[1], S.D. Henry[1], R. Bartenschlager[3], H.W. Tilanus[1], H.J. Metselaar[2]. Depts of Surgery[1] and Gastroenterology & Hepatology[2], Erasmus MC-University Medical Center, Rotterdam, The Netherlands and Dept of Molecular Virology[3], University of Heidelberg, Germany

13.00 TIPS outcome and its determinants *(p. 70)*
E. Bos[1], V. Williams[2], E. van der Linden[2], B. van Hoek[1]. Dept of Gastroenterology and Hepatology[1], and Dept of Radiology[2], Leiden University Medical Center, The Netherlands

13.15 Polytetrafluoroethylene (ePTFE) Covered and Uncovered Stents for TIPS in Budd-Chiari Syndrome: a Single Center Experience *(p. 71)*
S. Darwish Murad[1], P.M.T. Pattynama[2], H.R. van Buuren[1], S.J.G.C Frerichs[2], H.L.A. Janssen[1]. Depts of Gastroenterology & Hepatology[1] and Radiology[2], Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands

13.30 Preservation of the steatotic donor liver: machine perfusion versus cold storage *(p. 72)*
M. Bessems, B.M. Doorschodt, T.M. van Gulik. Surgical Laboratory, Dept of Surgery, Academic Medical Center, Amsterdam, The Netherlands

13.45 Efficacy of interferon-alpha for the treatment of lamivudine resistant chronic HBeAg-positive Hepatitis B virus infection. *(p. 73)*
W.F. Leemans[1], H.J. Flink[1], H.L.A. Janssen[1], H.G.M. Niesters[2], S.W. Schalm[1], R.A. de Man[1]. Depts of Gastroenterology & Hepatology[1] and Virology[2], Erasmus MC, University Medical Center Rotterdam, The Netherlands

14.00 Hepatic function assessed by 99mTc-mebrofenin scintigraphy correlates with liver histopathology in rat model of steatosis and steatohepatitis *(p. 74)*
R. Vetelainen[1], R. Bennink[2], C. De Bruin[2], AK van Vliet[1], TM van Gulik[1]. Depts of surgery[1] (Surgical laboratory) and Nuclear Medicine[2] Academic Medical Center, Amsterdam,The Netherlands

14.15 Polycystic liver disease is associated with PRKCSH and SEC63 mutations *(p. 75)*
E. Waanders[1], R.A. de Man[2], R.H.M. te Morsche[1], J.B.M.J. Jansen[1], J.P.H. Drenth[1]. Depts of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre[1] and Erasmus MC, University Medical Centre Rotterdam[2], The Netherlands

14.30 Evaluation of limited sampling strategy of ciclosporin-monitoring after liver transplantation using an individualized population pharmacokinetic model *(p. 76)*
P. Langers[1], S.C.L.M. Cremers[2], E.M.T. Rijnbeek[1], J. Ringers[3], C.H.B.W. Lamers[1], J. den Hartigh[2], B. van Hoek[1]. Dept of Gastroenterology & Hepatology[1] and Clinical Pharmacy & Toxicology[2] and Surgery[3], Leiden University Medical Center, The Netherlands

14.45 Ex vivo gene therapy of the liver: new approach to tackle hepatitis C infection and recurrence after liver transplantation *(p. 77)*
S.D. Henry[1], P.G. van der Wegen[2], H.J. Metselaar[3], R. Bartenschlager[4], H.W. Tilanus[1], B.J. Scholte[2], L.J.W. van der Laan[1]. Depts of Surgery[1], Cell Biology[2] and Gastro-enterology and Hepatology[3], Erasmus MC-University Medical Center, Rotterdam, The Netherlands and Dept of Molecular Virology[4], University of Heidelberg, Germany

15.00 Theepauze en ledenvergadering

Nederlandse Vereniging voor Hepatologie **Parkzaal**

SYMPOSIUM:
'Lever-update ter ere van lever-iconen: Van Berge Henegouwen en Schalm'

Voorzitters: P.L.M. Jansen en H.L.A. Janssen

Voordrachten in het Nederlands.

15.30 *Hepatitis C: Lange termijn follow-up van antivirale therapie.*
B.J. Veldt, afd. Maag-, Darm- en Leverziekten, Erasmus MC, Rotterdam

15.50 *Hepatitis B management: Zijn alle problemen opgelost?*
R.A. de Man, afd. Maag-, Darm- en Leverziekten, Erasmus MC, Rotterdam

16.10 *Portale hypertensie: Professor, have we come full circle? 40 jaar portale hypertensie, van shunt naar shunt.*
H.R. van Buuren, afd. Maag-, Darm- en Leverziekten, Erasmus MC, Rotterdam

16.30 *Primaire scleroserende cholangitis: Hoe maligne complicaties te behandelen en te voorkomen.*
F. Vleggaar, afd. Maag-, Darm- en Leverziekten UMC, Utrecht

16.50 *Galstenen en biliaire pancreatitis: Management en preventie*
K.J. van Erpecum, afd. Maag-, Darm- en Leverziekten UMC, Utrecht

17.10 *NASH: clinical implications (Engels)*
P. Portincasa, University of Bari, Italy

17.30 Congresborrel en diner

Presidential Selection - plenaire sessie **Brabantzaal**

Voorzitter: J.B.M.J. Jansen

Voordrachten in het Nederlands, spreektijd 10 minuten, discussietijd 5 minuten.

20.00 Interleukin-10 producing Lactococcus lactis for the treatment of Crohn's disease. *(p. 78)*
H. Braat[1], P. Rottiers[2], N. Huyghebaert[3], E. Remaut[2], J-P. Remon[3], S. van Deventer[1], S. Neirynck[2,4], M.P. Peppelenbosch[5], L.S. Steidler[2,4] and D.W. Hommes[3]. Dept of Experimental Internal Medicine1, Academic Medical Center Amsterdam, The Netherands, Dept for Molecular Biomedical Research[2] and Lab of of Pharmaceutical Technology [3], Ghent University, Belgium, Alimentary Pharmabiotic Centre[4], University College Cork, Cork, Ireland, Dept of Cell Biology[5], University of Groningen and Dept of Gastroenterology[6], Academic Medical Center Amsterdam, The Netherlands.

20.15 Five year's subjective and objective results of antireflux surgery: A randomized controlled trial of laparoscopic versus conventional Nissen fundoplication *(p. 79)*
W.A. Draaisma[1], H.G. Rijnhart-de Jong[1], I.A.M.J. Broeders[1], A.J.P.M. Smout[2], J. Oors[2], J. van der Scheur[2], E.J.B. Furnee[1], H.G. Gooszen[1,]2. Dept of Surgery[1] and Gastrointestinal Research Unit[2], University Medical Center Utrecht, The Netherlands

20.30 Arginine, citrulline, and nitric oxide metabolism in patients with Liver Failure and the effect of intervention with Hypothermia and transplantation *(p. 80)*
S.W. Olde Damink[1], S. Sen[2], R.P. Mookerjee[2], P.C. Hayes[3], N.E.P. Deutz[1], R. Jalan[2]. Dept of Surgery[1], Maastricht University, The Netherlands, Institute of Hepatology[2], UCL, and Royal Infirmary[3], Edinburgh, United Kingdom

20.45 Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis; A prospective randomised trial *(p. 81)*
D.L.Cahen[1], D.J. Gouma[2], Y. Nio[3], M. Delhaye[4], E.A.J. Rauws[1], M.A. Boermeester[2], O.R. Busch[2], J. Stoker[3], J.S. Laméris[3], M.G.W. Dijkgraaf[5], K. Huibregtse[1], J. Devière[4], M.J. Bruno1. Dept of Gastroenterology and Hepatology[1], Surgery[2] and Radiology[3], Academic Medical Centre, Amsterdam, The Netherlands. Dept of Gastroenterology and Hepatology[4], Hôpital Erasme, Brussels, Belgium, Dept of Clinical Epidemiology and Biostatistics[5], Academic Medical Centre Amsterdam, The Netherlands

21.00 **Altana lecture**
verzorgd door Prof. R.J. Nicholls, London, U.K.
'Restorative Proctocolectomy in 2005' *(p. 82)*

21.30 Ledenvergadering Nederlandse Vereniging voor Gastroenterologie

22.00 **Borrel in Bar Metro**, aangeboden door Altana Pharma BV, AstraZeneca BV Ferring BV, Olympus Nederland BV, Schering Plough BV en Tramedico BV.
U wordt door genoemde firma's van harte uitgenodigd hierbij aanwezig te zijn.

Casuïstiek voor de Klinikus **Brabantzaal**

Voorzitter: W. Hameeteman.

08.30 Casuïstische presentaties

09.00 Einde programma

Sectie Gastrointestinale Endoscopie **Brabantzaal**

Voorzitter: W. Hameeteman

Voordrachten in het Nederlands, spreektijd 7 minuten, discussietijd 3 minuten.

09.00 High-Resolution Endoscopy Is More Important Than Chromoendoscopy or Narrow Band Imaging For Detecting High grade Intraepithelial Neoplasia (HGIN) in Barrett Esophagus: A Prospective Randomized Cross-Over Study *(p. 85)*
M.A. Kara[1], F.P. Peters[1], W.D. Rosmolen[1], K.K. Krishnadath[1], F.J.W. ten Kate[2], A.C. Bultje[3], P. Fockens[1], J.J.G.H.M. Bergman[1]. Depts of Gastroenterology and Hepatlogy[1], Pathology[2] and Biostatistics and Epidemiology[3], Academic Medical Center Amsterdam, The Netherlands

09.10 Double balloon enteroscopy: The Dutch one year Experience. Indications, Yield, and Complications in a series of 125 cases *(p. 86)*
G.D.N. Heine[1], M. Hadithi[1], M.J.M. Groenen[2], E.J. Kuipers[2], M.A.J.M. Jacobs[1], C.J.J. Mulder[1]. Dept of Gastroenterology[1], VU University Medical Center, Amsterdam, Dept of Gastroenterology and Hepatology[2], Erasmus MC, University Medical Center Rotterdam, The Netherlands

09.20 The prevalence of K-ras mutations in ductal brush cytology and bile of subjects without pancreatic disease using the epidemiologic necropsy as study design *(p. 87)*
N.T. van Heek[1], E. Caspers[2], M. Tascilar[2], A. Musler[2], M. Polak[2], D.J. Gouma[1], P. Drillenburg[2], G.J.A. Offerhaus[2]. Depts of Surgery[1] and Pathology[2], Academic Medical Center Amsterdam, The Netherlands

09.30 Attendance at surveillance endoscopy in patients with adenoma or colorectal cancer *(p. 88)*
S.A. Mulder[1], M.E. van Leerdam[2], R.J.Th. Ouwendijk[1], R.W.M. Giard[3], D.J. Bac[1], E.J. Kuipers[2]. Dept of Internal Medicine[1], Ikazia Hospital, Dept of Gastroenterology and Hepatology[2], Erasmus MC, Dept of Pathology[3], Medical Centre Rijnmond Zuid and Ikazia Hospital, Rotterdam, The Netherlands

09.40 Correlation of a simple endoscopic scoring system of rectal wall toxicity with dose surface maps after prostate irradiation *(p. 89)*
D.J. de Jong[1], L.P. van der Vight[2], E.N.J.Th van Lin[2], A.L Hoffmann[2], M.E.P. Philippens[2], A.G. Visser[2]. Depts of Gastroenterology & Hepatology[1] and Radiation Oncology[2], Radboud University Nijmegen Medical Centre, The Netherlands.

09.50 The role of video capsule edoscopy in the diagnosis and management of Crohns disease. *(p. 90)*
K.F. Bruin[1], K.M.A.J. Tytgat[2], E.M. Mathus-Vliegen[1], D.W. Hommes[1], P. Fockens[1]. Dept of Gastroenterology[1], Academic Medical Center, Amsterdam and Dept[2] of Gastroenterology, Medical Center Alkmaar, The Netherlands

10.00 Koffiepauze

MINI-SYMPOSIUM: *'Chronische pancreatitis: Facts and Fiction'*

Voorzitters: Dr. M.J. Bruno en Dr. H.M. van Dullemen

10.30 Medicamenteuze behandeling
Dr. J.P.H. Drenth, afdeling Maag-, Darm- en Leverziekten, Universitair Medisch Centrum Nijmegen

10.55 Endoscopische behandeling
D.L. Cahen, afdeling Maag-, Darm- en Leverziekten, Ziekenhuis Amstelveen

11.20 Chirurgische behandeling
H.S. Hofker, afdeling Chirurgie, Universitair Medisch Centrum Groningen

11.45 Einde programma

12.00 Lunch in de expositiehal

Nederlandse Vereniging voor Gastroenterologie **Baroniezaal**

Bespreking Richtlijn *"Oesofaguscarcinoom"*

Voorzitter: P.D. Siersema

08.30 Inleiding
P.D. Siersema

8.35 Stadiëring oesofagscarcinoom
P.D. Siersema

8.55 Diagnostiek en behandeling vroeg carcinoom oesofagus
J.J.G.H.M. Bergmans

9.15 Niet-chirurgische behandeling oesofaguscarcinoom
A. van der Gaast

9.35 Chirurgische behandeling oesofaguscarcinoom
H.W. Tilanus

9.55 Conclusies

10.00 Einde programma

Nederlandse Vereniging voor Gastroenterologie **Baroniezaal**

Voorzitters: E.C. Klinkenberg en C.J.J. Mulder

Voordrachten in het Nederlands, spreektijd 7 minuten, discussietijd 3 minuten.

10.30 Evidence illustrating the need for dysplasia screening in patients with longstanding achalasia *(p. 91)*
G.E. Boeckxstaens[1], C.B. Verkleij[1], J.J. Bergman[1], J.F. Bartelsman[1], J. Offerhaus[2], G.N. Tytgat[1]. Depts of Gastroenterology[1] and pathology[2], Academic Medical Center Amsterdam, The Netherlands

10.40 Use of acid suppressive drugs by patients with Barrett's esophagus reduces the risk of esophageal adenocarcinoma. *(p. 92)*
P.J.F. de Jonge[1], L.M.M. Wolters[1], E.J. Kuipers[1], P. Honkoop[1], E.W. Steyerberg[2], P.D. Siersema[1]. Depts of Gastroenterology & Hepatology[1] and Public Health[2], Erasmus MC University Medical Center Rotterdam, The Netherlands

10.50 Length of Barrett's esophagus is determined by size of a hiatus hernia and use of proton-pump inhibitors *(p. 93)*
M. Kerkhof[1], E.W. Steyerberg[2], J.G. Kusters[1], E.J. Kuipers[1], P.D. Siersema[1], for the CYBAR-study group. Depts of Gastroenterology and Hepatology[1] and Public Health[2], Erasmus MC, Rotterdam

11.00 Ultrasound or CT scan for the detection of supraclavicular lymph nodes in patients with esophageal carcinoma *(p. 94)*
E.P.M. van Vliet[1], A. van der Lugt[2], E.J. Kuipers[1], H.W. Tilanus[3], A. van der Gaast[4], P.D. Siersema[1]. Depts of Gastroenterology[1], Radiology[2], Surgery[3] and Oncology[4], Erasmus MC/University Medical Center Rotterdam, The Netherlands

11.10 Neoadjuvant selective COX-2 inhibition downregulates important oncogenic pathways in patients with esophageal adenocarcinoma. *(p. 95)*
J.B. Tuynman[1,2], C.J. Buskens[1], K. Kemper[2], F.J.W. ten Kate[3], G.J.A. Offerhaus[3], D.J. Richel [2], J.J.B. van Lanschot[1]. Depts of surgery[1], Medical Oncology[2] and Pathology[3], Academic Medical Center, Amsterdam, The Netherlands

11.20 Barrett's esophagus is associated with a predominant humoral immune response *(p 96)*
L.M.G. Moons[1], J.G. Kusters[1], E. Bultman[1], E.J. Kuipers[1], W.H.M. Tra[1], J. Kwekkeboom[1], H. van Dekken[2], A.H.M. van Vliet[1], P.D. Siersema[1]. Dept of Gastro-enterology & Hepatology[1] and Pathology[2], Erasmus MC, Rotterdam, The Netherlands

11.30 The prognostic distinction between Barrett's oesophagus with and without specialised intestinal metaplasia is irrational. *(p. 97)*
M. van Blankenstein[1], C.W.N. Looman[2]. Depts of Gastroenterology & Hepatology[1] and Public Health[2], Erasmus MC, Rotterdam, The Netherlands

11.40 The Role of Autofluorescence Endoscopy for the Detection of High Grade Intraepithelial Neoplasia (HGIN) in Patients with Barrett Esophagus (BE). (Final report Maag Lever Darm Stichting project no. WS 01-63) *(p. 98)*
M.A. Kara[1], M.E. Smits[1], W.D. Rosmolen[1], A.C. Bultje[2], F.J.W. ten Kate[3], P. Fockens[1], G.N.J. Tytgat[1], R.S. DaCosta[4], C. Streutker[5], N.E. Marcon[6], B.C. Wilson[4], J.J.G.H.M. Bergman[1]. Depts of Gastroenterology[1], Clinical Epidemiology and Biostatistics[2] and Pathology[3], Academic Medical Center Amsterdam, The Netherlands, Dept of Medical Biophysics[4], Princes Magaret Hospital, Toronto, Canada, Dept of Pathology[5] and Center for Therapeutic Endoscopy & Endoscopic Oncology[6], St Michael's Hospital, Toronto, Canada

11.50 Multi-Band Mucosectomy; a new and easy technique for widespread mucosal resection. A feasibility study in 17 patients with a Barrett esophagus. *(p. 99)*
F.P. Peters[1], M.A. Kara[1], W.D. Rosmolen[1], F.J.W. ten Kate[2], K.K. Krishnadath[1], P. Fockens[1], J.J.G.H.M. Bergman[1]. Depts of Gastroenterology[1] and Pathology[2], Academic Medical Center, Amsterdam, Netherlands

12.00 Lunchbuffet in de expositiehal

Vrije voordrachten Sectie Experimentele Gastroenterologie **Parkzaal**

Voorzitter: G. Dijkstra en A.H.M. van Vliet

Voordrachten in het Nederlands, spreektijd 7 minuten, discussietijd 3 minuten.

08.30 Topical administration of activated protein C reduced coagulation and improved survival in experimental polymicrobial peritonitis *(p. 100)*
S.Q. van Veen[1], A.K. van Vliet[1], T.M. van Gulik[1], M.A. Boermeester[1]. Dept of Surgery (Surgical Laboratory)[1], Academic Medical Center of the University of Amsterdam, The Netherlands

08.40 Contribution of the mucosal immune system to methotrexate induced intestinal damage* *(p. 101)*
B. de Koning[1,2], D. Lindenbergh-Kortleve[1], J. van Dieren[1], L. de Ruiter[1], T. Matsumoto[3], R. Pieters[2], H. Büller[1], A. Einerhand[1], J. Samsom[1], E. Nieuwenhuis[1]. Lab of Pediatrics, Div of Pediatric Gastro-enterology[1] and Pediatric Oncology[2], Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands, Dept of microbiology[3], Toho University School of Medicine, Tokyo, Japan

08.50 CD4+ T lymphocytes mediate colitis induced by non-pathogenic Bacteroides vulgatus in HLA-B27 transgenic rats *(p. 102)*
F. Hoentjen[1,2], S.L. Tonkonogy[3], L.A. Dieleman[1,4], B. Feng Qian[1], B. Liu[1], J.D. Taurog[5], R. Balfour Sartor[1]. Depts of Gastroenterology and Hepatology, University of North Carolina[1], Chapel Hill, USA; Free University Medical Center[2], Amsterdam, The Netherlands; North Carolina State University[3], Raleigh, NC, USA; and University of Texas Southwestern Medical Center[5], TX, USA. Present address: Dept of Gastroenterology[4], University of Alberta, Edmonton, Canada.

09.00 Spontaneous development of colitis in mice deficient for Mucin 2* *(p. 103)*
M. van der Sluis[1,2], B.A.E. de Koning[1], A. Velcich[3], I. van Seuningen[4], H.A. Büller[1], J. Dekker[1], I.B. Renes[2], A.W.C. Einerhand[1] Paediatric Gastroenterology and Nutrition[1], Neonatology, Laboratory of Paediatrics[2], Erasmus MC-Sophia, Rotterdam, The Netherlands, Dept Oncology[3], Albert Einstein Cancer Center/ Montefiore Medical Centre, New York USA, Unité INSERM No560[4], Lille Cedex, France

09.10 Immune stimulating effects of oat β-glucan on enterocytes *in vitro*. *(p. 104)*
J.D. Ramakers[1], J.J. Volman[1], G. Önning[2], M. Biörklund[2], R.P. Mensink[1], J. Plat[1]. Dept of Human Biology[1], Maastricht University, Maastricht, The Netherlands and Div of Biomedical Nutrition[2], Lund University, Lund, Sweden

09.20 The prebiotic combination inulin/oligofructose prevents colitis in HLA-B27 rats by immunomodulation and changes in intestinal microflora *(p. 105)*
F Hoentjen[1,2], G.W. Tannock[3], C.J. Mulder[2], L.A. Dieleman[4]. Dept of Medicine[1], University of North Carolina at Chapel Hill, USA, Dept of Gastroenterology[2], Free University Medical Center, Amsterdam, The Netherlands, Dept of Agriculture and Forestry[3], University of Alberta, Edmonton, Canada, Dept of Gastroenterology[4], University of Alberta, Edmonton, Canada

09.30 Essential role for c-Raf in steroid insensitive Crohn's disease *(p. 106)*
M. Lowenberg[1], A. Verhaar[1], B. van den Blink[1], S. van Deventer[1], M. Peppelenbosch[2], D. Hommes[1,3]. Lab of Experimental Internal Medicine[1] and Dept of Gastroenterology[3], Academic Medical Center, Amsterdam, Dept of Cell Biology[2], University of Groningen, The Netherlands

09.40 Possible mechanism of action of tacrolimus in IBD: inhibition of NKT cell- and Intestinal epithelial cell- activation*. *(p. 107)*
J.M. van Dieren[1], C.J. van der Woude[1], M.E.H. Lambers[2], E.J. Kuipers[1], E.E. Nieuwenhuis[3]. Dept of Gastroenterology & Hepatology[1], Lab of pediatric Gastro-enterology[2] and Dept of Pediatric Gastroenterology[3] Erasmus MC, University Medical Center Rotterdam, The Netherlands

09.50 Turbo-probiotics as a tool for cell-based (mucosal) delivery of interleukin-10. *(p. 108)*
H. Braat[1], L. Steidler[2], S. Neirynck[2], M.L. Kapsenberg[3], S.J.H. van Deventer[1], E.C. de Jong[3], D.W. Hommes[1]. Depts of Experimental Internal Medicine[1] and Cell Biology & Histology and Dermatology[3], Academic Medical Center, Amsterdam The Netherlands, Alimentary Pharmabiotic Centre[2], University College Cork, Cork, Ireland

10.00 Koffiepauze

10.30 CARD15 in inflammatory bowel disease and Crohn's disease phenotypes: an association study and pooled analysis *(p. 109)*
L.E. Oostenbrug[1], I.M. Nolte[2], E. Oosterom[2], G. van der Steege[2], G.J. te Meerman[3], H.M. van Dullemen[1], J.P.H. Drent[4], D.J. de Jong[4], K. van der Linde[5], P.L.M. Jansen[6], J.H. Kleibeuker[1]. Depts of Gastroenterology and Hepatology[1], Medical Biology[2] and Medical Genetics[3], University Medical Center Groningen, Dept of Gastroenterology and Hepatology[4], University Medical Center St. Radboud, Nijmegen, Dept of Gastro-enterology and Hepatology[5], University Medical Center Erasmus, Rotterdam, Dept of Gastroenterology and Hepatology[6], Academic Medical Center, Amsterdam, The Netherlands

10.40 NOD2/CARD15 modulates specific Toll-like receptor pathways for the induction of cytokine release *(p. 110)*
D.J. de Jong[1], M.G. Netea[2], B.J. Kullberg[2], T. Jansen[2], L. Jacobs[2], M. Kramer[3], A.H.J. Naber[1], J.P.H. Drenth[1], G.J. Adema[3], J.W.M. van der Meer[2]. Depts of Gastroenterology and Hepatology[1], Medicine[2] and Tumor Immunology[3], Radboud University Nijmegen Medical Center, The Netherlands

10.50 Functional Consequences of NOD2 Deficiency in Crohn's Disease Patients Peripheral Blood Monocytes Derived Dendritic Cells *(p. 111)*
Z. Zelinkova[1], F. de Kort[1], I. Pronk[1], A. te Velde[1], M. Peppelenbosch[1], S. van Deventer[1], D. Hommes[2]. Lab of Experimental Internal Medicine[1] and Dept of Gastroenterology[2], Academic Medical Center Amsterdam, The Netherlands

Voorzitter: H.W. Verspaget

11.00 **INTERNATIONAL TEACHING SESSION**
Onderwerp: Gene Therapy

Prof. dr. J. Prieto, Division Hepatology and Gene Therapy,
University of Navarra, Pamplona, Spain.
"The promise of gene therapy in hepato-gastrointestinal disorders"

12.00 Lunchbuffet in de expositiehal

Nederlandse Vereniging voor Gastroenterologie **Brabantzaal**

SYMPOSIUM COLONKANKERSCREENING

Voorzitters: F.M. Nagengast en E. Dekker

13.30 Prof. dr. A. Verbeek (epidemioloog-arts, UMCN).
CRC screening, what can we learn from breast cancer screening?

14.00 Dr. R. Reij (college van zorgverzekeringen).
Organization of a national screening programme

14.30 Dr. K. Mach (Oberpullendorf, Austria).
The CRC screening model from Burgenland, Austria

15.00 Einde programma

Nederlandse Vereniging voor Gastroenterologie **Baroniezaal**

Voorzitters: J.J.G.H.M. Bergman en P. Siersema

Voordrachten in het Nederlands, spreektijd 7 minuten, discussietijd 3 minuten.

13.30 Barrett Esophagus (BE) with High-Grade intraepithelial neoplasia (HGIN) and/or Early Cancer (EC): Stepwise Radical Endoscopic Resection (SRER) for Complete Removal of the BE Is Safe and Effective *(p. 112)*
F.P. Peters[1], M.A. Kara[1], W.D. Rosmolen[1], F.J.W. ten Kate[2], K.K. Krishnadath[1], J.J.B. van Lanschot[3], P. Fockens[1], J.J.G.H.M. Bergman[1]. Depts of Gastroenterology[1], Pathology[2], and Surgery[3], Academic Medical Center, Amsterdam, Netherlands

13.40 Endoscopic ultrasonography (EUS) for staging of esophageal cancer in a non-expert EUS center *(p. 113)*
E.P.M. van Vliet[1], M.J.C. Eijkemans[2], J.W. Poley[1], E.W. Steyerberg[2], E.J. Kuipers[1], P.D. Siersema[1]. Depts of Gastroenterology[1] and Public Health[2], Erasmus MC/University Medical Center Rotterdam, The Netherlands

13.50 Detection of severe neoplasia in Barrett's esophagus using autofluorescence endoscopy *(p. 114)*
J. Haringsma, J.W. Poley, I.M. Kerkhof, H. van Dekken, P. Blok, E.J. Kuipers. Dept of Gasroenterology[1] and Pathology[2], Erasmus MC University Medical Center, Rotterdam, The Netherlands

14.00 Intraluminal oxygen prevents mucosal ischemic damage in a new model of complete local small bowel ischemia in pigs *(p. 115)*
P.B.F. Mensink[1], C. Kruse[2], J.J. Kolkman[1], B. Reszel[3], U. Holscher[3], A. de Weerd[4], G Knichwitz[2]. Dept of Gastroenterology[1], Medical Spectrum Twente, The Netherlands, Dept of Anesthesiology[2], Universital Hospital Muenster, Germany, University of Apllied Sciences[3], Steinfurt, Germany, Medical Measurement Systems[4], Enschede, The Netherlands

14.10 Genome wide response to starvation in the mouse small intestine *(p. 116)*
M. Sokolovic[1], T. Hakvoort[1], D. Wehkamp[2], L. Gilhuijs-Pederson[2], R. van Haaften[3], C. Evelo[3], A. van Kampen[2], W.H. Lamers[1]. AMC Liver Centre[1] and Bioinformatics Laboratory[2], Academic Medical Centre, Amsterdam; BiGCaT Bioinformatics[3], University of Maastricht, The Netherlands

14.20 A Prospective Study Comparing Video Capsule Endoscopy Followed by Double Balloon Enteroscopy for Suspected Small Bowel Disease *(p. 117)*
M. Hadithi, G. Dimitri N. Heine, M.A.J.M. Jacobs, A.A. van Bodegraven, C.J. Mulder. Dept of Gastroenterology, VU University Medical Center, Amsterdam, The Netherlands

14.30 Double balloon enteroscopy in Peutz Jeghers diseaseFirst experience with a new diagnostic and therapeutic tool *(p. 118)*
G.D.N. Heine[1], M.H.A. Hadithi[1], M.J.M. Groenen[2], E.J. Kuipers[2], A.A. van Bodegraven[1], M.A.J.M. Jacobs[1] and C.J.J. Mulder[1]. Depts of Gastroenterology and Hepatology, VU University Medical Center[1], Amsterdam and Erasmus MC University Medical Center Rotterdam[2], The Netherlands

14.40 FDG-PET detects malignant degeneration of duodenal adenomas in familial adenomatosis polyposis patients and can change clinical management. *(p. 119)*
M.C.A. van Kouwen[1], H.J. van Krieken[2], H. van Goor[3], W.J.G. Oyen[4], J.P.H. Drenth[1], F.M. Nagengast[1]. DeptS of Gastroenterology and Hepatology[1], Pathology[2], Surgery[3] and Nuclear Medicine[4], Radboud University Nijmegen Medical Centre, The Netherlands

14.50 Tumour progression in colorectal cancer: array-CGH analysis of the 8q22-q23, 13q21-q31 and 20q amplicons *(p. 120)*
B. Carvalho[1], C. Postma[1], S. Mongera[1], M.A.J.A. Hermsen[2], B. Ylstra[3], G.A.Meijer[1]. Depts of Pathology[1] and Microarray core facility[3], VU University Medical Center, Amsterdam, The Netherlands and IUOPA[2] - Hospital central de Asturias, Oviedo, Spain

15.00 Theepauze

Vrije voordrachten Sectie Experimentele Gastroenterologie **Parkzaal**

Voorzitter: J.G. Kusters en H.W. Verspaget

Voordrachten in het Nederlands, spreektijd 7 minuten, discussietijd 3 minuten.

13.30 The secondary bile acid deoxycholic acid induces differential expression of chemokines in the progression of Barrett's esophagus to adenocarcinoma *(p. 121)*
D.A. Bax, L.M.G. Moons, E.J. Kuipers, F. Kariem, J. Haringsma, A.H.M. van Vliet, J.G. Kusters, P.D. Siersema. Dept of Gastroenterology and Hepatology, Erasmus MC - University Medical Center Rotterdam, The Netherlands

13.40 Indomethacin disrupts protective effect of phosphatidylcholine against bile salt-induced ileal mucosa injury. *(p. 122)*
N.G. Venneman[1], M. Petruzzelli[1,2], J.E. van Dijk[3], A. Verheem[1], L.M.A. Akkermans[1], A.B.A. Kroese[1,4], K.J. van Erpecum[1]. Gastrointestinal Research Unit[1], Depts of Gastroenterology and Surgery, and Dept of Medical Physiology[4], University Medical Center Utrecht, Utrecht, The Netherlands; Section of Internal Medicine[2], Dept of Internal and Public Medicine, University of Bari Medical School, Bari, Italy, Dept of Pathobiology, Division Pathology[3], Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands

13.50 Efficient detection of genetic abnormalities in Barrett's esophagus patients by automated analysis of DNA FISH on brush cytology specimens. *(p. 123)*
A. Rygiel[1], J.J.G.H.M. Bergman[2] J.W.P.M van Baal[1], F. Milano[1], M.P Peppelenbosh[3], K. K. Krishnadath[2]. Lab of Experimental Internal Medicine[1] and Dept of Gastroenterology and Hepatology[2], Academic Medical Center Amsterdam and Dept of cell biology[3], Rijks Universiteit Groningen, The Netherlands

14.00 Fine-mapping of the coeliac disease linkage region on chromosome 19p13 reveals a new player in the field *(p. 124)*
A.J. Monsuur, I. Lavrijsen, A. Zhernakova, L. Franke, C. Wijmenga. Complex Genetics Section, DBG-Department of Medical Genetics, University Medical Center Utrecht, The Netherlands

14.10 The transcriptomes of Barrett's esophagus and normal esophageal squamous epithelium by Serial Analysis of Gene Expression (SAGE). *(p. 125)*
J.W.P.M. van Baal[1], K.K. Wang[2], F. Milano[1], A.M. Rygiel[1], J.J.G.H.M. Bergman[3], S.J.H. van Deventer[1], M.P. Peppelenbosch[4], K.K. Krishnadath[3]. Depts of Experimental Internal Medicine[1] and Gastroenterology & Hepathology[3], Academic Medical Center, Amsterdam, The Netherlands, Dept of Gastroenterology and Hepathology[2], Mayo foundation, Rochester, USA, and Dept of Cell Biology[4], Rijksuniversiteit Groningen, Groningen, The Netherlands

14.20 Expression profiles of the recovering intestinal mucosa in coeliac disease point towards arrested terminal differentiation of enterocytes that contribute to the clinical pleiotropy*. *(p. 126 + 127))*
B. Diosdado[1], M. Wapenaar[1], H. van Bakel[1], L. Franke[1], J. Meijer[2], M.L. Mearin[3], C. Mulder[4], C. Wijmenga[1]. DBG-Department of Medical Genetics[1], University Medical Center Utrecht, Dept of Pathology[2], Rijnstate Hospital, Arnhem, Dept of Pediatrics[3], Leiden University Medical Center and Dept of Gastroenterology[4], VU Medical Center, Amsterdam, The Netherlands

14.30 MET signalling in primary colon epithelial cells leads to increased transformation irrespective of aberrant Wnt signalling. *(p. 128)*
E.M.J. Boon[1], M. Kovarikova[2], P. Derksen[1], R. van der Neut[1]. Dept of Pathology[1] Academic Medical Center, Amsterdam, The Netherlands, Institute of Biophysics[2], Acad. Sci. Czech Rep., Brno, Czech Republic

14.40 TRAIL induces apoptosis in human colorectal adenomas and human colorectal adenoma cell lines *(p. 129)*
M. Jalving[1,2], J.J. Koornstra[1,2], S. de Jong[2], N. Zwart[3], W. Boersma-van Ek[1], J. Wesseling[3], E.G.E. de Vries[1], J.H. Kleibeuker[2]. Dept of Gastroenterology[2], University Medical Center Groningen, The Netherlands

14.50 The specificity of CDX-2 and cytokeratin expression as biomarkers in Barrett's esophagus *(p. 130)*
J.W.P.M. van Baal[1], F. Milano[1], A.M. Rygiel[1], A. Bozikas[1], J.J.G.H.M. Bergman[2], S.J.H. van Deventer[1], M.P. Peppelenbosch[3], K.K. Krishnadath[3], Dept. of Experimental Internal Medicine, AMC, Amsterdam[1], Dept of Gastroenterology and Hepathology, AMC, Amsterdam[2], Dept of Cell Biology, Rijks Universiteit Groningen, Groningen[4], The Netherlands

15.00 Einde programma

Symposium Vereniging Maag Darm Lever Verpleegkundigen **Auditorium**

De IBD patiënt: leven met een chronische darmontsteking

09.30	Ontvangst met koffie/thee
10.00	Welkomswoord en inleiding door de voorzitter van de VMDLV: dhr. H. Welling
10.05	Ledenvergadering door dhr. H. Welling
10.20	Anatomie, fysiologie en pathologie mbt. IBD, behandeling van colitis ulcerosa en de ziekte van crohn met remicade door dr. D. de Jong van het UMCN.
11.00	*koffie/thee*
11.15	Chirurgische mogelijkheden bij de ziekte van crohn en colitis ulcerosa en de stomazorg door mevr. E. Geerards / mevr. H. Vroomen: nurse practioner colo-rectale chirurgie van het UMCN.
12.15	*Lunch*
13.15	Patiënt empowerment en IBD poli. door dhr. dr. H. Festen en mevr. I. Kappé
14.15	Het belang van de Crohn en colitis vereniging. door mevr T. Markus, directeur van de Crohn en colitis vereniging
14.35	Het verhaal van een patiënt een ervaringsdeskundige
14.55	Afsluiting van de dag door dhr. H Welling
15.00	Einde programma

Sectie Endoscopie Verpleegkundigen en Assistenten **Diezezaal**

10.30	O*ntvangst, koffie*
11.00	Belang van optimale handhygiene Mevr. K. Smits, endoscopieverpleegkundige, Gelre Ziekenhuis, Apeldoorn
11.20	Endoscopie op kinderleeftijd Dhr. H. Tichelaar, endoscopieverpleegkundige, Gelderse Vallei Ziekenhuis, Ede
11.40	Helicobacter ademtest Mevr. M. van Voorst, endoscopieverpleegkundige, Haga Ziekenhuis locatie Leyenburg, Den Haag
12.00	Ledenvergadering SEVA
12.30	*Lunchbuffet in de expositiehal*
13.30	Familiaire belasting erfeljke tumoren Dhr. dr. H.F.A. Vasen, internist, Stichting Opsporing Erfelijke Tumoren, Leiden
14.00	Anatomie en fysiologie van de pancreas Prof. dr. J.B.M.J. Jansen, Universitair Medisch Centrum St. Radboud, Nijmegen
14.30	Pancreas cystes Mevr. M. Thompson, endoscopieverpleegkundige, Academisch Medisch Centrum, Amsterdam
15.00	*Koffie/thee, einde programma*

A prospective analysis of patients with adenocarcinoma of the gastric cardia and lymph node metastasis in the proximal field of the chest

S.M. Lagarde[1], H.A. Cense[1], J.B.F. Hulscher[1], H.W. Tilanus[2], F.J.W. ten Kate[3], H. Obertop[1], J.J.B. van Lanschot[1]. Depts of Surgery[1] and Pathology[3], Academic Medical Centre at the University of Amsterdam, Dept of Surgery[2], Erasmus Medical Centre Rotterdam, The Netherlands

Patients with an adenocarcinoma of the cardia and lymph node metastasis in the proximal field of the chest only have a chance for surgical cure with a transthoracic esophagectomy with extended lymphadenectomy. These positive nodes do not alter TNM staging, however it is unclear if these relatively distant metastases have an effect on long term survival. Therefore, the aim of this study was to identify the incidence of nodal metastasis in the proximal field of the chest in patients with gastric cardia adenocarcinoma and to evaluate the prognostic significance of these positive lymph nodes. Between 1994 and 2000 a right sided transthoracic esophagectomy for adenocarcinoma of the cardia was performed in 50 patients as part of a randomized trial. Eleven patients (22%) had lymph node metastasis in the proximal field of the chest. These patients had significantly more positive nodes counted ($p = 0.020$). The median survival in patients with lymphatic dissemination in the proximal field was 8 months in comparison to 25 months for patients with negative lymph nodes in this field ($p = 0.009$). Multivariate analysis revealed that the presence of positive nodes in the proximal field is an independent prognostic indicator for survival.In conclusion, lymphatic dissemination in the proximal field of the chest is a common phenomenon and an indicator of poor prognosis in patients with adenocarcinoma of the cardia. Preoperative detection of lymph node metastasis in the proximal field of the chest changes operative treatment in patients with gastic cardia adenocarcinoma. To achieve a radical resection a transthoracic esophagectomy must be performed, but even after this extended procedure these patients have a poor prognosis. Therefore, (neo-) adjuvant chemoradiation should be tested to improve long-term outcome.

Additional Value of Positron Emission Tomography in Preoperative Staging of Esophageal Cancer: a Prospective Cohort Study

M. Westerterp[1], H.L. van Westreenen[2], G.W. Sloof[3], P.L. Jager[4], O.S. Hoekstra[5], E.F.I. Comans[5], H. Groen[6], P.M.M. Bossuyt[7], J. Stoker[8], H.M. van Dullemen[9], P. Fockens[10], E.J. van der Jagt[11], J.J.B. van Lanschot[1], J.Th.M. Plukker[2]. Depts of Surgery[1], Clinical Epidemiology & Biostatistics[7], Nuclear Medicine[3], Gastroenterology[10] and Radiology[8], Academic Medical Center, Amsterdam, Dept of Nuclear Medicine[5], VU University Medical Center, Amsterdam, Office for Medical Technology Assessment[6], Depts of Surgery[2], Nuclear Medicine/PET-center[4], Gastroenterology[9] and Radiology[11]; Groningen University Medical Center, The Netherlands

The exact role of Positron Emission Tomography using 18F-fluorodeoxyglucose (PET) on selection of esophageal cancer (EC) patients for curative treatment is still unknown. Therefore, we prospectively studied PET in EC patients after a state-of-the-art conventional preoperative work-up focusing on the detection of distant dissemination precluding surgery with curative intent.This prospective non-randomized cohort study was performed in 2 academic medical centers specialized in EC surgery. The eligible patients had histologically proven cancer of the esophagus or gastro-esophageal junction. All patients were staged with Multidetector Computed Tomography, Endoscopic Ultrasound and cervical ultrasonography, both combined with Fine Needle Aspiration on indication. Patients who had no evidence of distant metastases and/or locally irresectable disease on conventional preoperative work-up were included in this study to undergo additional PET. Primary endpoint was percentage of prevented, futile esophagectomies. Between October 2002 and July 2004, 199 patients were included in this study. PET revealed additional hotspots suspected for metastatic disease in 34 of 199 patients (positivity rate 17%). Several types of additional investigations were performed for verification of these lesions. In 8 patients, distant metastases were histologically confirmed and thus unnecessary esophagectomy was prevented. In 2 of these patients, explorative laparotomy was necessary for their histological confirmation. Therefore, PET led to upstaging in 8 patients (4%). Moreover, FDG-PET detected synchronous neoplasia in 11 patients (8 adenomas and 1 adenocarcinoma of the colon; 1 Hürthle tumor: 1 thyroid adenoma), not interfering with EC treatment. The remaining 15 patients with a suspicious FDG-lesion turned out to be false positive (i.e. clinically irrelevant). After conventional work-up, PET revealed distant metastases in 4% of the patients with EC, precluding potentially curative resection.

Extracapsular lymph node involvement in patients with adenocarcinoma of the distal esophagus and gastroesophageal junction

S.M. Lagarde[1], D. de Boer[1], F.J.W. Ten Kate[2], O.R.C. Busch[1], H. Obertop[1], J.J.B. van Lanschot[1]. Depts of Surgery[1] and Pathology[2], Academic Medical Centre at the University of Amsterdam, The Netherlands

The relevance of extracapsular lymph node involvement has poorly been studied in patients with adenocarcinoma of the distal esophagus and gastroesophageal junction. Therefore, the aim of this study was to identify the incidence and prognostic significance of extracapsular lymph node involvement in these patients. Between 1993 and 2002 a transthoracic or transhiatal esophagectomy for adenocarcinoma of the distal esophagus or gastroesophageal junction was performed in 301 patients. 206 patients had lymphatic dissemination (69%). In these patients a median of 17 (range 2-67) lymph nodes were resected and a median of 5 (range 1-31) positive nodes were identified. All positive lymph nodes were reexamined by a pathologist to determine tumor extent beyond the lymph node capsule. In 141 (68%) of the N1-patients extracapsular lymph node involvement was identified. Extracapsular lymph node involvement was associated with a more advanced T-stage, more resected nodes ($p=0.002$), more positive nodes ($p<0.001$) and a higher lymph node ratio ($p=0.001$). There was a significant difference in median survival between patients with extracapsular lymph node involvement and patients with intracapsular lymph node involvement (median 12 versus 36 months resp.) ($p<0.001$). In a multivariate analysis, extracapsular lymph node involvement as well as lymph node ratio were independent prognostic indicators for survival.In conclusion, extracapsular lymph node involvement is a common phenomenon in patients with adenocarcinoma of the distal esophagus or gastroesophageal junction. It is an indicator of advanced disease and poor prognosis. Presently there is no staging modality that can differentiate between intra- and extracapsular lymph node involvement preoperatively. To improve long term outcome in patients with extracapsular lymph node involvement, adjuvant radiotherapy could be tested.

Minimally invasive approach in acute necrotising pancreatitis: a strategy for a selected subgroup or a potential benefit for all? Dutch Acute Pancreatitis Study Group

M.G.H. Besselink[1], H.C. van Santvoort[1], T.L. Bollen[2], M.S. van Leeuwen[1], J.S. Lameris[3], S.P. Strijk[4], Van der Jagt[5], H.S. Hofker[5], C.H. Dejong[6], Boermeester[3], Van Ramshorst[2], A.F.M. Schaapherder[7], C.J.H. van Eijck[8], J.P.E.N. Pierie[9], M.A. Cuesta[10], J.F. Lange[11], H. van Goor[4], H.G. Gooszen[1] for the Dutch Acute Pancreatitis Study Group. Depts of Surgery and Radiology: University Medical Center Utrecht[1], St. Antonius Hospital Nieuwegein[2], Academic Medical Center Amsterdam[3], University Medical Center St.Radboud[4], University Hospital Groningen[5], University Hospital Maastricht[6], Leiden University Medical Center[7], Erasmus Medical Center Rotterdam[8], Medical Center Leeuwarden[9], Free University Medical Center Amsterdam[10], Medical Center Rijnmond Zuid, Rotterdam[11]

It has been suggested that minimally invasive procedures (MIP), as opposed surgical drainage and necrosectomy via laparotomy, can only be applied in a selected subset of acute pancreatitis patients. As part of preparations for a multicenter randomised trial, this study investigated the potential applicability of MIP. Pre- and postoperative clinical data were collected retrospectively from 106 consecutive patients operated for severe acute pancreatitis between 2000 and 2003. Five radiologists, aware of the timing of the CT-scan, post hoc judged feasibility and safety of placing a drain into the collections. The preferred route was the left retroperitoneum. Collections were classified as accessible for MIP if placement of a 14 F guidance drain was feasible. The radiologists were also asked whether the drain would produce more than 50 ml. Finally, the radiologists were asked to classify the collections according to the Atlanta definitions (fluid collection, abscess, pancreatic necrosis, pseudocyst or a mixture).CT-scans of 80 patients were available. Placement of a 14 F drain was deemed feasible and safe in 83% of cases (mean % per radiologist). Only in 2 cases all radiologists agreed that placement of a drain was not possible, because no clear collections was visible. In 57% of all patients a drain could be placed from the left retroperitoneum. In majority of cases (64%, range 49-82%) the radiologists expected >50 ml drain production. The five radiologists only agreed in 3 cases (4%) on the Atlanta definition of the collection. In 15 cases four of the five radiologists agreed. Conclusion: MIP in case of (peri-)pancreatic necrosis seems feasible in the vast majority of patients with severe acute pancreatitis. A randomised controlled trial were MIP is being testing will only be minimally frustrated by “not-includable” patients. Inter-hospital communication will be troublesome due to the limited capacity of the Atlanta definitions to classify collections.

Risk Adjusted Prediction of Operative Morbidity in Patients undergoing Pancreatoduodenectomy with the use of POSSUM

S.M.M. de Castro, J.T. Houwert, K.F.D. Kuhlmann, O.R.C. Busch, T.M. van Gulik, H, Obertop, D.J. Gouma. Dept of Surgery, Academic Medical Center, Amsterdam, The Netherlands

Reports on comparison of operative morbidity rates after pancreatoduodenectomy between units may be misleading because it does not account for the physiological variation of the condition of the patient. The aim of the study was to evaluate the applicability of the Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (POSSUM) for patients who undergo pancreatoduodenectomy and to look for specific risk factors associated with morbidity in a high volume center.Between January 1993 and December 2003, 511 patients underwent a pancreatoduodenectomy of which 424 (83%) for malignant disease. POSSUM was calculated according to the generally accepted criteria. The performance of POSSUM was evaluated by assessing the "goodness-of-fit" using the exponential analysis method using observed to predicted morbidity (O:P) ratio. Predictive factors of interest associated with morbidity were analyzed using Univariate an Multivariate analysis.Overall, 285 of 511 patients (51%) had one or more complication after pancreatoduodenectomy and 7 patients (1.4%) died. The O:P ratio for POSSUM was 1.09. In Multivariate analysis, four statistically significant factors associated with an increased morbidity ($p<0.05$) were identified: hypertension (OR = 1.86, 95%CI:1.10-3.14), advanced age >76 years (4th quartile) (OR = 1.73, 95%CI:1.01-2.95), male gender (OR = 1.56, 95%CI:1.05-2.94) and ampulla of Vater adenocarcinoma (OR = 1.66, 95%CI:1.01-2.75). Overall, POSSUM performed well and may serve as a useful comparative audit tool for patients who undergo pancreatoduodenectomy. A dedicated PAN-POSSUM model can be made by adjusting for tumor pathology since this was the only factor which was not incorporated in POSSUM.

Prophylactic probiotics reduce bacterial translocation in experimental pancreatitis

F. Lutgendorff, L.P. van Minnen, H.M. Timmerman, H.G. Gooszen, L.M.A. Akkermans. Gastrointestinal Research Unit, Depts of Gastroenterology and Surgery, University Medical Center Utrecht, The Netherlands

Secondary infection of pancreatic necrosis is considered the major cause of mortality in patients with severe acute pancreatitis. Bacteria translocated from the gut are often held responsible for these infections. Pathophysiological factors for translocation are bacterial overgrowth, mucosal barrier failure and impaired immune defences. Ecologic 641, a mixture of six probiotic strains, has proven to modulate these factors in vitro. Aim of this study was to determine whether prophylactic multispecies probiotics are capable of effectively reducing bacterial translocation and mortality in experimental pancreatitis.
Pancreatitis was induced in male Spraque-Dawley rats (n=36) by standardized intraductal bile salt infusion (glycodeoxycholate, 15 mM) followed by pancreatic hyperstimulation (intravenous cerulein, 5µg/kg/hr, for 6 hours). All animals were randomly allocated in two groups; placebo or probiotics were administered daily via a permanent gastric canula, five days prior to and seven days after induction of pancreatitis. Surviving animals were sacrificed after seven days for microbiological analysis of mesenteric lymph nodes (MLN), spleen, liver and pancreatic tissue.
Probiotics significantly reduced bacterial translocation to the MLN, liver, spleen and pancreas compared to placebo (2.83 vs. 3.50 10Log CFU/gram, P=0.04; 3.17 vs. 4.84 10Log CFU/gram, P=0.04; 2.96 vs. 4.02 10Log CFU/gram, P=0.02; 3.55 vs. 5.73 10Log CFU/gram, P=0.02 respectively). Probiotic treatment numerically decreased mortality by 44%, compared to placebo (4/17 (24%) vs. 10/22 (45%)).
In conclusion: in experimental acute pancreatitis, prophylactic probiotics significantly decrease bacterial translocation to the MLN, liver, spleen and pancreas, and numerically decrease mortality.

Synergistic effect of interstitial laser coagulation and doxorubicin in a murine model for solitary colorectal liver metastasis.

L.M. Veenendaal, R. van Hillegersberg, N. Smakman, J.D.W. van der Bilt, O. Kranenburg, I.H.M. Borel Rinkes. Dept of Surgery, University Medical Center Utrecht, The Netherlands

Interstitial laser coagulation (ILC) is gaining acceptance for treatment of irresectable colorectal liver metastases. However, local recurrence rates are still high. To overcome this problem we investigated the potential of adjuvant systemic therapy after ILC in a murine model.Liver metastases were established by subcapsular implantation of C26-luciferase colon-carcinoma fragments (1x1mm) in the liver of 32 Balb/c mice. Animals were randomly allocated to one of four treatments groups (n=8 per group), A) sham treatment, B) 1 mg/kg doxorubicin injections, C) ILC (Nd:YAG, 6W/cm, 400J), D) ILC (Nd:YAG, 6W/cm, 400J) followed by 1 mg/kg doxo-rubicin injections. At different time points tumor load was measured by non-invasive in vivo bioluminescent imaging. At day 28 mice were sacrificed and immunohisochemistry was performed with HE and NADH (marker of mitochondrial viability) staining. Groups A and B demonstrated an exponential increase in tumor load. Mice treated with ILC showed an initial decrease of tumor size, followed by recurrent tumor growth after 5 days in 7/8 mice (88%). This was confirmed by HE and NADH staining. The group treated with combined ablation and doxorubicine demonstrated no recurrence at all (8/8 mice).
Conclusions: We were able to establish a murine model for solitary liver metastases in which recurrent tumor arises after ILC treatment. Combi-nation of interstitial laser coagulation and doxorubicin had a strong synergistic effect leading to complete remission. These results provide a solid base for further investigation of combined treatment of chemotherapy and ILC for colorectal metastases.

Ischemia/reperfusion accelerates the outgrowth of hepatic micrometastases in a highly standardized murine model

J.D.W. van der Bilt[1], E.A. te Velde[1], M.W. Nijkamp[1], N. Smakman[1], L.M. Veenendaal[1], E.E. Voest[2], P.J. van Diest[3], O. Kranenburg[1], R. van Hillegersberg[1] and I.H.M. Borel Rinkes[1]. Dept of Surgery[1], Medical Oncology[2] and Pathology[3], University Medical Center Utrecht, The Netherlands

During liver surgery, hepatic ischemia/reperfusion (I/R) injury often occurs due to vascular clamping. The adverse effects of I/R on hepatocellular damage and postoperative liver function are well documented. The influence on the outgrowth of residual micrometastases is unknown. We investigated the effect of hepatic I/R on the outgrowth of pre-established colorectal micrometastases in a highly standardized murine model and evaluated the putative protective effect of alternative clamping methods. Five days following intrasplenic injection with C26 colon carcinoma cells the vascular structures to the left lobe were clamped for 45 minutes under hemodynamically stable conditions. Markers of oxidative stress (GSH), liver cell damage (ALT/ AST) and tumor growth were assessed over time. Next, we analyzed the effect of ischemic preconditioning, intermittent clamping and selective clamping of the portal vein on hepatocellular damage and tumor growth. I/R induced oxidative stress and hepatocellular damage as measured by decreased liver GSH, a marked increase in liver enzymes and the presence of hepatic necrosis covering 14% of the parenchyma. The outgrowth of micrometastases in occluded liver lobes was accelerated 5-6 fold when compared to non-occluded liver lobes and was associated with the presence of necrotic areas. Both early and late heaptocellular damage were prevented by occluding blood flow intermittently or by portal clamping as indicated by a 96% reduction in liver enzymes and by the absence of necrosis. In addition, accelerated tumor growth was completely prevented by both methods. In contrast, although early liver cell damage was largely prevented (87%), ischemic preconditioning reduced hepatocellular necrosis only by 50% and failed to protect against accelerated tumor growth.Our results identify I/R as a strong stimulus of recurrent intrahepatic tumor growth and indicate that protection against I/R-induced tissue necrosis cross-protects against this phenolmenon.

First experiences with the use of Imatinib in gastro-intestinal stromal tumours

M.F. Ernst[1], S. Rodenhuis[2], F. van Coevorden[1]. Dept of Surgical[1] and Medical[2] Oncology The Netherlands Cancer Institute / Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands

Gastro-intestinal stromal tumours (GIST) are non-epithelial, infrequent tumours of the gastro-intestinal tract; most frequently they are found in the stomach and small bowel. At presentation almost 50% of the patients have metastases; after initial curative surgery almost half of these patients develop local disease or metastases. Surgical resection is the procedure of choice. However, with the introduction of Imatinib Mesylate (Glivec), an increase in survival can be expected. Against this background we looked at the indications for surgical and medical therapy and we reviewed our first experiences in patients with a GIST, treated with Imatinib.From December 2000 till September 2004 36 consecutive patients with a locally advanced, irresectable or metastatic GIST were included; all tumours were c-KIT positive. Response after Imatinib treatment was defined as stable disease or partial response. Thirteen patients did not undergo initial surgery and 27 patients had metastases at presentation. After Imatinib a response was seen in 32 (88%) patients: 13 patients (36%) had stable disease – with a decrease of complaints – and 19 (52%) patients had detectable partial response. Progressive disease was only seen in 2 (6%) patients; 2 (6%) patients died of peritonitis shortly after the start of Imatinib, due to tumour necrosis. During follow-up 13/36 patients had an indication for surgery after Imatinib. After a median follow-up of 24 months, 14 patients have died and 18/22 patients still use Imatinib. Conclusions: In the “Imatinib-era” surgery plays an important role in the primary operable GIST. For operable GIST with intermediate or high malignancy a randomised EORTC study (E62024) has been developed: this study evaluates the value of adjuvant (postoperative) Imatinib. Imatinib is primary choice if a patient has an irresectable or metastatic GIST; in case of good response surgery can be considered.

A clinical prediction model to select patients with secondary peritonitis for relaparotomy

B. Lamme[1], O. van Ruler[1], D.J. Gouma[1], J.B. Reitsma[2], M.A. Boermeester[1]. Depts of Surgery[1] and Epidemiology & Biostatistics[2], Academic Medical Center Amsterdam, The Netherlands

The decision when to perform a relaparotomy after initial laparotomy for secondary peritonitis is largely subjective and experience-based. To date there is no reliable scoring system that aids the decisional process by predicting relaparotomy outcome. Our aim was to develop an objective prediction model for a positive relaparotomy in the acute phase of secondary peritonitis. The study population (n=220) with secondary peritonitis was derived from a retrospective cohort. For prediction of positive findings at relaparotomy patients with a positive relaparotomy (n=62) were compared to patients undergoing a negative relaparotomy (n=55) and patients recuperating without the need for relaparotomy after index laparotomy (n=103). A prediction model was constructed from a binary logistic regression model by the subsequent accumulation of patient, peritonitis, operative and postoperative variables, assessed on clinical judgment and statistical analysis. The probability of a positive relaparotomy was 62/220 (28%). Forty-seven percent of all relaparotomies (55/117), being 25% (55/220) of all patients, had negative findings. The accumulation of predictors in various models resulted in an increase in ROC curves. Patient variables (model A) resulted in a ROC curve with an area under the curve (AUC) of 0.60 [95%CI 0.52-0.68]. Adding peritonitis variables (B) increased the AUC to 0.73 [95%CI 0.66-0.80]. The addition of operation variables (C) did not make a valuable contribution [AUC 0.73; 95%CI 0.67-0.81]. The final model (D) including selected patient, peritonitis, operative and postoperative predictors was associated with a ROC curve with an AUC of 0.87 [95%CI 0.82-0.92] and showed good calibration and discrimination. The sensitivity was 76% and specificity 83% with a total error rate of 15%.
Conclusions: This model may help to recognize patients likely to have a positive relaparotomy and reduced the error rate from 25% to 15%. Further external validation and development of a prediction rule is needed in a prospective, cross-sectional series.

Long-term outcome in terms of Quality of life (QOL), small bowel obstruction, body image and cosmesis after hand-assisted laparoscopic (HAL) vs open proctocolectomy with ileal pouch-anal anastomosis (IPAA): a randomised trial

S.W. Polle[1], M.S. Dunker[1], J.F.M. Slors[1], D.J. Gouma[1], D.W. Hommes[2], W.A. Bemelman[1]. Depts of Surgery[1] and Gastroenterology[2], Academic Medical Center Amsterdam, The Netherlands

Short-term results after HAL vs open proctocolectomy with IPAA for familial adenomatous polyposis or ulcerative colitis didn't show any difference in a randomised trial. Aim of this study was to assess long-term results in terms of QOL, significant small bowel obstruction, body image and cosmesis. All 60 patients included in this trial were sent SF36 and GIQLI questionnaires one year after surgery. Body image (BIQ) and Photoseries (PSQ) questionnaires together with questions regarding readmission were sent separately. The PSQ included 4 photographs of incisional scars of 2 open and HAL procedures. Patients were asked to grade their incisional scars and those on the photographs (scale 1 to 10). One year QOL data was available for 53 patients (26 HAL, 27 open). QOL scores were improved compared to three months without any difference between the groups. Forty-six patients (23 HAL, 23 open) were followed for 2.7 years median (1.4 - 5.5 years). Of 8 patients who were readmitted 7 had small bowel obstruction (4 HAL, 3 open) and 1 incisional hernia (former stoma site, HAL group). Of the HAL group 2 patients underwent reoperation (1 incisional hernia, 1 bowel obstruction) vs 2 of the open group (2 bowel obstruction). A significant difference was found on the cosmetic scale of the BIQ ($P = 0.002$) but not on the body image scale. The HAL group rated their scar higher than the open group (mean 7.9 vs 5.7, $P < 0.001$). After seeing photographs of the same and alternative procedure, the open group rated their scar lower (mean 5.4, $P=0.30$) and the HAL group similarly. Of the HAL group 97.4% would prefer a HAL approach vs 60% of the open group if the same operation would be necessary (60% were willing to pay a personal fee). At one year QOL improves compared to 3 month follow-up irrespective of the type of surgery. HAL surgery is significantly associated with better cosmesis compared to open surgery. Most patients prefer a HAL approach and are willing to pay for it.

Excellent results with The Self Expanding Metal Stent as a bridge to surgery

R.J.I. Bosker[1], E.H. Eddes[1], F. ter Borg[2], M. Ledeboer[2], M.M.J.J.R. Jaspers[3], M. Eeftinck Schattenkerk[1]. Depts of Surgery[1], Gastroenterology[2] and Radiology[3], Deventer Hospital, The Netherlands

Acute surgery for colonic obstruction has higher mortality and morbidity and worse survival rates than elective colorectal surgery. Endoscopic insertion of a Self Expanding Metal Stent (SEMS) effectively decompresses the obstructed colon and converts an emergent surgical procedure to an elective procedure. In the mean time synchronous lesions and distant metastasis can be excluded, the bowel can be cleaned, the patient's medical status can be optimised and the patient can receive neoadjuvant therapy. In this study we present our experiences with the Bridge to Surgery Technique(BTS). From July 2003 to December 2004, 18 consecutive patients, who presented with acute colonic obstruction (F:M=11:7) were treated with insertion of a SEMS under endoscopic guidance. After insertion biopsies were taken. All procedures were without complications. The colon proximal to the obstruction was examined using a barium enema. A CT-scan of the thorax and abdomen provided preoperative staging criteria to select cases suitable for elective surgical resection. In patients with massive distant metastasis, unresectable local disease or unacceptable surgical risk the stent was considered as definitive palliative treatment. Four patients were not operated because of massive distant metastasis(3) and unacceptable surgical risk(1). In the remaining 14 patients (F:M=9:5, mean age 77 (56-90) year) an elective resection, sigmoidectomy(5), left(3) and right(4) hemicolectomy, transversum resection(2), with primary anastomosis without the formation of a stoma was performed. The postoperative cause was uneventful in all cases. The mean hospital stay after surgery was 11 (7-18) days.There for we advise the BTS technique over acute emergency surgery for acute colonic obstruction.

Identification of the signal transduction mechanism mediating the anti-inflammatory effect of vagal nerve stimulation

E.P.M. van der Zanden[1], W.J. de Jonge[1], G.E. Boeckxstaens[1,2]. Motility center[1] and Dept of Gastroenterology[2], Academic Medical Center, Amsterdam, The Netherlands

Postoperative ileus (POI) is mediated by inflammation of the intestinal muscularis, a mechanism triggered by bowel manipulation activating macrophages. We recently showed that vagal nerve stimulation prevents POI by inhibition of intestinal macrophages via nicotinic receptor activation. Here, we studied the nicotinic actylcholine receptor (nAchR) subtype and unraveled the unknown downstream signaling pathway involved.Resident peritoneal macrophages were isolated from Balb/C mice by peritoneal lavage. Cytokine levels were measured in cells pretreated with nicotine (0-10μM) and challenged with LPS (100 ng/mL). Moreover, nicotine treated cells were used for Western blotting or immunoprecipitation. In peritoneal macrophages, nicotine significantly ($p<0.05$) reduced LPS-induced release of the pro-inflammatory mediators TNFα, MIP2 and IL6 (51.2+/-4.4%, 20.6+/-18.1% and 39.3+/-13.9% vs. control), but IL10 levels were unaffected. This anti-inflammatory effect of nicotine was associated with activation of Stat3 and its downstream gene Socs3. The nicotine-induced Stat3/Socs3 activation and IL6 release inhibition were blocked by pretreatment with the non-selective nAchR antagonist hexamethonium (ED50 8.3*10-9 M), or the α7 nAchR blocker methyllocaconitine (ED50 5.0*10-8 M). Next, the role of Jak-2 was studied, since this is an important Stat3 activator. AG490, a specific Jak-2 inhibitor, blocked the nicotine-induced Stat3 phosphorylation. Interestingly, co-immunoprecipitation experiments reveal an association between the α7 nAchR and Jak-2 in cells treated with nicotine, indicating that this receptor recruits Jak-2.We conclude that resident intestinal macrophages are inhibited by the 'cholinergic anti-inflammatory pathway', involving activation of the α7 nAchR and subsequent activation of the Jak-2/Stat3/Socs3 cascade. Our data indicate nicotinic receptor activation as a novel target in the treatment of POI and problably other inflammatory disorders.

Gastric cancers in young and old patients have different genomic profiles

T.E. Buffart[1], B. Carvalho[1], E. Hopmans[1], V. Brehm[2], E. Klein Kranenbarg[2], B.M. Visser[1], B. Ylstra[3], C.J.H. van de Velde[2], G.A. Meijer[1]. Dept of Pathology[1] and Micro-array Core Facility[3], VU University Medical Center, Amsterdam and Dept of Surgery[2], Leiden University Medical Center, The Netherlands

Gastric cancer in young patients has been associated with a more aggressive behavior and poorer prognosis, compared to older patients. We recently demonstrated that patterns of DNA copy number alterations in gastric cancer correlated with clinical outcome (Weiss et al., Oncogene 2003; 22:1872-1879). The present study aimed to compare such copy number alterations between gastric cancers of young (<50 years) and old (≥70 years) patients with high resolution at a whole genome scale.
DNA derived from 46 paraffin embedded gastric cancer tissue samples of 17 patients <50 years (median 43 (21-49)) and 29 patients ≥70 years (median 75 (70-83)) were analyzed by genome wide array-CGH using a BAC array of 5000 clones printed in triplicate. Patterns of chromosomal aberrations were analyzed by K-means cluster analysis of the normalized log2 tumor to normal fluorescence ratios of all (but the sex chromosomes derived) clones using TMEV software (www.tigr.org/software). Cluster membership was correlated to age.
K-means cluster analysis of the array-CGH results revealed two clusters with different genomic profiles that correlated significantly with age (p=0.003). Since gastric cancer cases from cluster one, with mainly young patients, showed a significantly higher incidence of lymph node metastasis compared to cluster two, with mainly elderly gastric cancer patients (P=0.04), a sub-group analysis was performed with lymph node positive cases only (young: n=12; elderly: n=20). Again, K-means cluster analysis yielded two clusters of tumors with different genomic profiles, where cluster membership correlated significantly with age (P=0.008).
Gastric cancers of young and old patients have different genomic profiles, and this is independent of lymph node status. This may well reflect different pathogenic mechanisms of the disease.

Polyethylene glycol (PEG) as a marker for gastrointestinal permeability: a novel assay, excretion kinetics, and sensitivity

A.P.M. Kerckhoffs[1], M.B.M. de Smet[2], M.G.H. Besselink[2], W. Renooij[2], L.M.A. Akkermans[2]. Dept of Gastroenterology[1] and Surgery[2], University Medical Center Utrecht, The Netherlands

Intestinal permeability is a key factor in small bowel bacterial overgrowth leading to bacterial translocation and sepsis. PEGs of various molecular mass have been used as markers for intestinal permeability: PEG 400 can freely pass the intestinal mucosal barrier, larger PEG molecules only if intestinal permeability is compromised. We developed an HPLC-based assay of PEGs using evaporative light-scattering detection allowing simultaneous quantitation of PEGs. We aimed to test the physiologic sensitivity of the assay by challenging the intestinal mucosal barrier with NSAIDs. Ten healthy volunteers drank a 100 mL solution of 5 g PEG 400, 1.5 g PEG 1500, 5 g PEG 4000 and 10 g PEG 10 000 in water before and after 2 days naproxen (750 mg/day). Urine was collected at 2-hour intervals for 24 hours. A standard lactulose-mannitol test was performed for comparison. Mucosal damage was evaluated from release of intestinal fatty acid binding protein (I-FABP). Changes in intestinal permeability were evaluated from areas under the PEG-excretion time-curves (AUC) and from the intestinal permeability index (IPI: % of initial dose of PEGs 1500, 4000, and 10 000 recovered in 24-hour urine relative to PEG 400). Excretion of PEGs 400 and 1500 peaked within 2 hours after ingestion; PEG 4000 peaked at 4 hours; PEG 10 000 was not identified in urine. Naproxen did not influence peak excretion times of PEGs and had no effect on extent of excretion of PEGs 400 and 1500. Naproxen significantly increased excretion of PEG 4000 (AUC's: $p < 0.05$; IPI: $p < 0.05$). Naproxen increased lactulose-mannitol ratio's significantly ($p < 0.01$) but mostly still to values within the normal range (ratio < 0.03). Naproxen did not cause release of I-FABP indicating no extensive mucosal damage.
Conclusion: 2-days ingestion of naproxen compromised intestinal permeability to the extent of allowing passage of PEG molecules up to the size of 4000, while the intestine is still impermeable for PEGs the size of 10 000.

The role of TRAIL-mediated apoptosis in the development of colorectal cancer and possibilities for treatment and prevention (Final report Maag Lever Darm Stichting project WS 01-31)

J.J. Koornstra[1], M. Jalving[1], F.E.M. Rijcken[1], S. de Jong[2], H. Hollema[3], E.G.E. de Vries[2], J.H. Kleibeuker[1]. Depts of Gastroenterology and Hepatology[1], Medical Oncology[2] and Pathology[3], University Hospital Groningen, The Netherlands

TNF-related apoptosis-inducing ligand (TRAIL) is a recently discovered cytokine, which induces apoptosis upon binding to its pro-apoptotic receptors DR4 and DR5. Targeting of these receptors, e.g. by TRAIL, is considered a promising anti-neoplastic strategy. We aimed to determine the immunohistochemical expression of DR4 and DR5 in normal colon epithelium (n=10), colorectal adenomas (n=165) and carcinomas (n=81), concerning both sporadic and hereditary (HNPCC and FAP) cases. Next, we investigated the importance of BAX mutations in tumours with microsatellite instability (MSI) as BAX has been reported to play a role in TRAIL-mediated apoptosis. For this purpose, MSI-positive colorectal cancer cases with (n=36) or without (n=6) BAX mutations were studied. Furthermore, we examined the possibility to induce apoptosis in adenoma cells in vitro and in ex vivo cultures of adenoma tissue. Finally, we studied effects of the NSAID sulindac on apoptosis and expression of TRAIL receptors in normal colon, as recent data suggested that this pathway is involved in the chemopreventive effect of sulindac. Almost all adenomas and carcinomas showed expression of DR4 and DR5, with intensity stronger than seen in normal epithelium, suggesting potential sensitivity to TRAIL-induced apoptosis. These results were obtained in sporadic cases as well as in hereditary cases. A few carcinomas (n=6) did not express DR4, all with mucinous histology. These tumours did however show expression of DR5. No differences in apoptosis, DR4 and DR5 expression were found between MSI-positive tumors with or without BAX mutations, not supporting a critical role for BAX mutations as a mechanism to evade TRAIL-induced apoptosis. In two adenoma cell lines (VACO-235 and VACO-330), TRAIL administration resulted in strong induction of apoptosis. Similar effects were observed in ex-vivo cultures of adenoma tissue. Sulindac administration in two populations, 18 HNPCC and 6 FAP patients, treated in chemoprevention trials, had no effect on apoptosis or TRAIL receptor expression in normal mucosa. Conclusion: Our results support the potential application of TRAIL or other TRAIL receptor agonists in strategies aimed to prevent or treat colorectal adenomas and carcinomas.

High-fat nutrition inhibits inflammation via the vagus nerve; a novel neuro-immunological pathway.

M.D.P. Luyer[1], W.A. Buurman[1], M. Hadfoune[1], J.A. Jacobs[2], C.H.C. Dejong[1], J.W.M. Greve[1]. Dept of Surgery[1], University Hospital Maastricht, The Netherlands

Previously, we showed that high-fat nutrition ameliorates various inflammatory processes, however, the underlying mechanism remained unknown. The processing of dietary fat and regulation of nutrition-related responses are predominantly controlled by the autonomic nervous system via the vagus nerve. Recently, the vagus nerve was also shown to inhibit the inflammatory response via efferent fibres. Here, we investigate whether the autonomic nervous system is implicated in the protective effect of high-fat enteral nutrition. Using a model of hemorrhagic shock, leading to inflammation and loss of gut barrier function, we studied the effect of (sham) vagotomy in fasted rats or rats fed with high-fat enteral. Hemorrhagic shock was induced by withdrawing 2.1 ml blood/100 gram body weight. Subsequently, plasma and tissue samples were collected after 90 minutes. TNF-α and IL-6 were determined via ELISA and intestinal permeability was assessed ex vivo by measuring horseradish peroxidase (HRP) leakage in an ileum-segment and by determining endo-toxin in plasma.The protective effect of high-fat enteral nutrition on circulating TNF-α and IL-6 levels following hemorrhagic shock (TNF: 5 ± 1 pg/ml, IL-6:19 ± 9 pg/ml) was abolished by vagotomy and comparable to those of fasted rats (TNF:205 ± 11 pg/ml ($p<0.01$), IL-6: 80 ± 5 pg/ml ($p<0.01$)). In line, vagtomized rats treated with high-fat nutrition showed an increased intestinal permeability (HRP:2.3 ± 0.1 mg/ml) and elevated endotoxin levels (28 ± 1 pg/ml) compared to sham-vagotomized rats (HRP:1 ± 0.1 mg/ml, $p<0.05$, endotoxin 12 ± 2 pg/ml, $p<0.05$).
In conclusion, these findings show a novel neuro-immunological pathway in which high-fat enteral nutrition ameliorates inflammation and preserves gut barrier function by activation of the autonomic nervous system.

Intestinal handling during surgery induces an inflammatory response in patients

F.O. The[1], R.J. Bennink[2], W.J. de Jonge[1], D.J. Gouma[3], M.P.M. Burger[4], G.E. Boeckxstaens[1]. Depts of Gastroenterology and Hepatology[1], Nucleair Medicine[2], Surgery[3] and Gynaecology[4], Academic Medical Center Amsterdam, The Netherlands

Introduction: Handling of the intestine during abdominal surgery results in inflammation of the intestinal muscularis, triggering inhibitory pathways that lead to postoperative ileus in mice. Previous studies showed that inflammatory mediators are also upregulated during abdominal surgery in man. However, to what extent intestinal handling per se is the trigger of this inflammatory response in man has not been investigated. Aim: 1. To evaluate the effect of intestinal handling on the upregulation of inflammatory mediators, and 2. to visualize surgery induced intestinal inflammation in patients using leukocyte scanning. Methods: 1. Quantitative mRNA analysis for ICAM-1, LFA-1, iNOS and TNF-alpha was performed on small intestinal tissue removed during a biliary reconstructive procedure. Non-handled tissue, resected at the start of the procedure, was compared with manipulated tissue removed at the end of the procedure. 2. Abdominal 99mTC-labelled leukocyte SPECT-CT scans were made 24h prior and 24h after surgery and expressed as bone marrow corrected ratio. Patients undergoing an abdominal hysterectomy (AH) were compared with those having a laparoscopic or trans-vaginal gynecological procedure (C). Results: 1. Three to four h after manipulation of the small intestine, mRNA levels were increased compared to non-handled intestine (LFA-1 5.1, ICAM-1 2.0, iNOS 6.3 and TNF-alpha 2.5 fold increase n=4). 2. Labeled leukocyte scanning showed an increase of activity in the abdominal cavity in AH patients (delta= 140.3 ± 12.9 % of preoperative scan, n=4) but not in C patients (delta = 109.3 ± 11.3 % of preoperative scan, n=3). Conclusion: Our results suggest that intestinal handling during surgery in patients initiates an up-regulation of inflammatory mediators and leads to an enhanced recruitment of leukocytes to the manipulated area. These data indicate that also in man manipulation-induced inflammation represents an important mechanism contributing to postoperative ileus.

Delayed visceral hypersensitivity in maternal separation depends on mast cell degranulation and is mediated by NGF and the nociceptor TRPV-1

R. van den Wijngaard, O. Welting, D. van der Coelen, W. de Jonge en G. Boeckxstaens. Dept of Gastroenterology, Academic Medical Center Amsterdam, The Netherlands

We have recently shown delayed visceral hypersensitivity in response to an acute stressor (1 hr water avoidance, WA) in maternal separated rats (MS), but not in non-separated (NH) control rats. The exact mechanisms underlying this delayed response are however unknown. Nerve growth factor (NGF), one of the mediators released by mast cells, is known to upregulate the nociceptor TRPV-1. In the present study, we therefore investigated the possible role of mast cells and hypothesized that the delayed hypersensitivity is mediated by TRPV-1 in response to mast cell derived nerve growth factor (NGF). MS and NH Long Evans pups were equipped with EMG electrodes in the abdominal muscles connected to a telemetry transmitter to record the visceromotor response (VMR) to colorectal distention. Visceral sensitivity was assessed by intermittent distention (1, 1.5, 2 ml) before and 24 hours after WA. Rats were pre-treated with either the mast cell stabilizer doxantrazole (20 mg/kg ip), anti-NGF (1 ml 1/2000 ip), TRPV-1 antagonist capsazepine (10 mg/kg ip) or placebo. Post-WA VMR to colorectal distention was calculated by setting the maximum value of the first (pre-WA) distension protocol at 100%.The VMR to colorectal distention significantly increased 24 hours after WA compared to pre-WA in MS (n=7, 151 ± 14 %, $p<0.002$, Wilcoxon signed ranks), but not in NH (n=7, 99 ± 7 %, NS) rats treated with placebo. Doxantrazole (n=7, 102 ± 9 %, NS), anti-NGF (n=8, 94 ± 6 %, NS) and capsazepine (n=4, 98 ± 6 %, NS) prevented the development of visceral hypersensitivity 24 hours after WA.Our data confirm that acute stress triggers the development of delayed visceral hypersensitivity in MS, but not in NH rats. We provide evidence that this hypersensitivity is mediated by NGF and the nociceptor TRPV1 and depends on mast cell degranulation. Based on these findings, we suggest that mast cell degranulation in response to WA induces visceral hypersensitivity via NGF mediated upregulation of TRPV-1.

The vagal anti-inflammatory pathway prevents postoperative ileus by nicotinic acetylcholine receptor activation on intestinal macrophages

W.J. de Jonge, E.P. van der Zanden, F.O. The, G.E. Boeckxstaens. Depts of Gastroenterology and Hepatology, Academic Medical Center Amsterdam, The Netherlands

Macrophage activation following surgical bowel manipulation mediates the development of post-operative ileus (POI). Acetylcholine released by efferent vagal signaling has been shown to down regulate macrophages. Here, we evaluated whether vagal nerve stimulation (VNS) prevents intestinal inflammation and POI by activating nicotinic acetylcholine receptors (nAchR) on intestinal macrophages in a murine model.
Mice underwent either laparotomy (L) or intestinal manipulation (IM), and/or electrical stimulation of the left cervical vagal nerve (VNS) for 5 min pre- and 15 min post-operatively (5 V, 2 ms, 5 Hz). Gastric emptying was determined as a readout for POI by scintigraphic imaging 24 hrs after surgery. Myeloperoxidase (MPO) activity was measured in ileal muscularis to assess inflammation. Peritoneal macrophages were treated with nicotine (0-10 µM) and/or LPS (100 ng/mL).
In IM control mice, post-surgical gastric emptying was significantly delayed compared to L control (gastric retention (%) at 60 min: 14.5 ± 2.7 (L) and 43.0 ± 6.7 (IM)). However VNS prevented this IM-induced gastroparesis (25.2 ± 3.2%, $p<0.05$). IM, but not L alone, led to a significant increase in MPO activity in intestinal muscularis (6.4+/-30.7 U/g (L) and 30.7+/-12.6 (IM), $p<0.05$) that was significantly reduced when combined with VNS (7.7+/-1,2 U/g, $p<0.05$). In intestinal segments pre-incubated with nicotinic receptor blocker hexamethonium (10-4 M), VNS failed to reduce IM-induced intestinal inflammation. Peritoneal macrophages expressed the alpha7 subunit of acetylcholine receptor, and nicotine dose-dependently inhibited the LPS-induced release of TNF-alphą, IL-6, and MIP2, but not IL10. This cytokine release inhibition was blocked by hexamethonium (ED50 8.3*10-9 M for IL6).
Conclusion. VNS ameliorates manipulation-induced inflammation and POI via inhibition of macrophage activation. The anti-inflammatory effect of VNS is brought about by activation of nicotinic receptors on intestinal macrophages.

Vitamin A equivalency of β-carotene in oil in healthy Dutch adults measured using specifically 13C-labelled β-carotene and retinol

C.A. Bouwman[1], C.E. West[1,2], R.B. van Breemen[3], D. Zhu[3], M. van Lieshout[4], E. Siebelink[2], P. Versloot[2] and T.H.J. Naber[1]. Dept of Gastroenterology[1], Radboud University Nijmegen Medical Centre and Dept of Human Nutrition[2], Wageningen University, The Netherlands, Dept of Medicinal Chemistry and Pharmacognosy[3], University of Illinois at Chicago, USA and Dept of Nutrition[4], North-West University, South Africa

Quantitative data on the absorption and the bioconversion of β-carotene to retinol in (healthy and diseased) humans in different diets is needed. Many research groups tried to estimate the conversion factor of β-carotene to retinol, but still there are few data in humans available about the vitamin A equivalency of dietary β-carotene. The objective is to quantify the vitamin A equivalency of β-carotene in oil using the plateau isotopic enrichment (PIE) technique. The PIE technique is based on reaching a plateau of isotopic enrichment during prolonged intake of multiple low doses of labelled β-carotene and retinol, where the level of the plateau depends on the concurrent increase of the body pool of unlabelled β-carotene and retinol. A controlled dietary intervention with 24 healthy Dutch adults was performed. The subjects consumed for 21 days a diet containing vegetables and fruit low in β-carotene with added synthetic β-carotene (4.5 mg/d) ('oil diet'). Every day capsules were consumed with the cooked meal containing 55 µg [$^{13}C_{10}$] β-carotene and 55 µg [$^{13}C_{10}$] retinyl palmitate. Fasting blood samples were taken and faeces was collected for 72 hours to measure the degree of isotopic enrichment of β-carotene with [$^{13}C_{10}$] β-carotene and of retinol with [$^{13}C_5$] retinol and [$^{13}C_{10}$] retinol using HPLC coupled with APCI LC-MS. The dose-corrected ratio of [$^{13}C_5$] to [$^{13}C_{10}$] retinol was used to determine the vitamin A equivalency of β-carotene in oil. Concentrations of carotenoids and retinol were measured in serum, faeces, vegetables and duplicate diets by HPLC. In this 'oil diet', 3.2 µg (95% CI 2.7-3.7) β-carotene in oil has the same vitamin A activity as 1 µg retinol. The bioefficacy of β-carotene in oil is 30%. These data are necessary to revise the current recommendations of vitamin A activity of β-carotene in oil.

Interorgan amino acid exchange across the intestines and the liver in surgical patients

M.C.G. van de Poll[1], M.P.C. Siroen[2], P.A.M. van Leeuwen[2], R.G.H. Beets[3], S.W.M. Olde Damink[1], G.C. Melis[2], P.G. Boelens[2], N.E.P. Deutz[1], P.B. Soeters[1], C.H.C. Dejong[1]. Depts of Surgery[1] and Radiology[3], Maastricht University and Dept of Surgery[2], VU University Medical Center Amsterdam, The Netherlands

Due to difficult accessibility of the portal vein, human data on hepatic and intestinal amino acid metabolism are limited. Data concerning the healthy liver are completely lacking. We aimed at studying interorgan amino acid exchange across the non-cirrhotic human liver. In 10 patients without cirrhosis undergoing surgery, blood was sampled simultaneously from a radial artery, hepatic vein and the portal vein. Amino acid and ammonia concentrations were measured to calculate arteriovenous differences (V-A). In 5 patients portal and hepatic arterial blood flow was measured using duplex to quantify metabolic flux ((V-A) x blood flow). In the others mean flow was used to calculate flux. There was significant intestinal uptake of glutamine and glutamate: (mean (SEM)) -39.4 (1.9) and -5.1 (1.6) µmol/kg/h respectively ($p<0.05$) and release of alanine, citrulline and ammonia: 17.3 (3.6), 5.1 (1.0) and 38.7 (10.4) µmol/kg/h ($p<0.005$). Intestinal flux of essential amino acids was insignificant ($p=0.44$). There was a stoichiometric correlation between intestinal glutamine uptake and ammonia release ($r2=0.41$, $p=0.046$). Hepatic ammonia uptake (-40.9 (12.3) µmol/kg/h) is directly related to intestinal ammonia production ($r2=0.94$, $p<0.001$) making total splanchnic ammonia release insignificant ($p=0.54$). Hepatic uptake of essential amino acids (25.2 (7.2) µmol/kg/h, $p=0.007$) reflects net hepatic protein synthesis in the postabsorptive state. Conclusion: This is the first report of amino acid and nitrogen exchange across the non-cirrhotic human liver. In these subjects the liver serves as an ammonia trap, metabolizing all intestinal-derived ammonia, making splanchnic ammonia release insignificant. The described method will be implemented in forthcoming experiments.

Continuous L-arginine infusion does not deteriorate the haemodynamic condition in patients with severe sepsis

Y.C. Luiking[1], M. Poeze[1], M. Hendrikx[2], P. Breedveld[1], C.H.C. Dejong[1], P.W. de Feiter[1], F. Rubulotta[2], G. Ramsay[2], N.E.P. Deutz[1]. Depts of Surgery[1] and Intensive Care[2], Maastricht University Hospital, The Netherlands

Septic patients have reduced plasma arginine levels, and have been considered arginine deficient. This has resulted in the use of L-arginine enriched enteral formulas, which recently raised much concern. These formula, however, contain also other components besides L-arginine. Arginine is the precursor for nitric oxide, which is known as a vasodilator. Since little is known about the haemodynamic effects of continuous intravenous L-arginine supplementation as a single component in sepsis, we aimed to study dose-response effects of L-arginine in patients with severe sepsis.

Eight ICU patients with severe sepsis/septic shock (sepsis<48h) were included. APACHE II scores ranged between 27-43 on admission. All patients received norepinephrine treatment. After 2h baseline measurements, L-arginine-HCl was infused continuously in 3 stepwise increased doses (0.6, 1.2, and 1.8 μmol/kg.min), each dose for 2h. Haemodynamics were recorded at 30-min intervals throughout the protocol. Blood samples were taken and analysed for plasma arginine levels by HPLC. Data are means±SEM; Repeated measurements ANOVA for statistics.

No significant changes in systemic and pulmonary blood pressure, and norepinephrine dose were observed. Compared with plasma arginine levels of age-matched healthy subjects (81 ± 5 μM), plasma levels were reduced in our patients (49 ± 2 μM; $P<0.05$), and increased to 192 ± 9 μM during the highest arginine dose. Heart rate decreased during arginine supplementation (from 101 ± 3 to 95 ± 6 b/min; $P<0.05$) and stroke volume increased (from 78 ± 3 to 88 ± 4 ml/beat; $P<0.05$).

Conclusion: Arginine infusion does not affect systemic and pulmonary blood pressure, but increases cardiac stroke volume. This indicates that continuous arginine supplementation does not deteriorate the haemodynamic condition in severe septic patients, despite its vasodilating effect.

(Supported by Novartis)

Functional Non-Retentive Faecal Soiling in children: 12 years of longitudinal follow-up

W.P. Voskuijl[1], J.B. Reitsma[2], R. van Ginkel[1], J.A.J.M. Taminiau[1], H.A. Büller[3], M.A. Benninga[1]. Dept of Paediatric Gastroenterology and Nutrition[1], Emma Children's Hospital, Dept of clinical epidemiology and biostatistics[2], Academic Medical Centre, Amsterdam, the Netherlands, Dept of Paediatrics[3], Sophia Children's Hospital, Rotterdam, The Netherlands

Background: Functional non-retentive faecal soiling (FNRFS), encopresis in the absence of signs of faecal retention, is a frustrating phenomenon in children and difficult to treat. It is assumed that FNRFS will resolve spontaneously beyond puberty, however no data on long-term outcome are available.
Aim: To investigate the very long-term outcome of FNRFS patients after intensive medical treatment.
Methods: Between 1990 and 1999, 119 patients (96 boys) with FNRFS were enrolled in 2 prospective, randomised trials investigating the effect of biofeedback training and / or laxative treatment. Thereafter, follow-up (FU) was performed at 6 months, 1 year and thereafter annually until the end of data collection in September 2004. A standardised questionnaire was used, either during clinical visit or by telephone, to evaluate symptoms. Success was defined as having less than 1 encopresis episode in 2 weeks while not using medication for more than 1 month.
Results: Median age at entry (25th-75th percentiles) was 9.2 (7.9-11.6) years and the median duration of symptoms before intake (25th-75th percentiles) was 4.4 (3.0-6.7) years. A 90% follow-up was achieved at all stages of the study. After 2 years of intensive behavioural and medical therapy, 33 out of 112 (29.5%) patients were successfully treated. The cumulative success percentage after 7 years of FU was 80%. At the biological ages of 12 and 18 years, 49.4% (40/81) and 15.5% (9/58) of the patients still had encopresis, respectively. Age at intake younger than 6 years in combination with secondary encopresis was associated with a lower chance of achieving success (HR: 0.51 (95% CI: 0.27-0.98), P=0.04). Relapse occurred in 37% of patients (cumulative percentage after 7 years), and occurred most likely in the first two years after an initial success.
Conclusions: Only 29% of the patients with FNRFS are successfully treated after two years of intensive treatment. Thereafter, a steady increase in success is observed. Nevertheless, at the age of 18 years, 15% still have encopresis.

Threonine incorporation into mucin 2 isolated from intestinal outflow fluid in neonates

M.W. Schaart, A.C.J.M de Bruijn, H. Schierbeek, I.B. Renes, J.B. van Goudoever. ErasmusMC/Sophia Children's Hospital, Rotterdam, the Netherlands

The small intestine is one of the most metabolically active tissues in the body. The small intestine utilizes 50-80% of the dietary threonine intake. The main component serving protection against infiltrating noxes and pathogenic bacterial insults is formed by the mucus layer. Mucus mainly consists of gel forming mucins. Mucin 2 (MUC2), the predominant intestinal mucin, is a large glycoprotein, rich in threonine-proline-serine tandem repeats. We hypothesized that dietary threonine is incorporated mainly into secreted proteins of the small intestine, especially MUC2.To determine the dietary threonine incorporation into MUC2 and to quantify the fractional synthesis rate (FSR) of MUC2 in neonates with a jejunostomy or ileostomy. Intragastric infusion of U-^{13}C labeled threonine was used to determine the incorporation of threonine into secreted MUC2 in the jejuno/ileal outflow fluid of 6 neonates. Small intestinal MUC2 was isolated using CsCl gradient ultracentrifugation. Fractions of these samples were analyzed using SDS-PAGE gels. Mucins in gel were stained with Periodic Acid/Schiff's(PAS) staining. The isotopic enrichment of threonine was measured in MUC2 using Gas Chromatography Isotopic Ratio Mass Spectrometry (GC-IRMS).Dietary threonine was incorporated into MUC2 of the small intestine. The delay in incorporation of threonine into collected MUC2 from the jejunostomy and ileostomy, after the introduction of U-^{13}C labeled threonine infusion, was 2-7 hours. The FSR varied between 900% and 3500% per day.
Conclusions: Dietary threonine is used for MUC2 synthesis. The minimum time to synthesize and excrete mucins is 2 hours. Mucins have a high turnover rate in infants with a jejunostomy or ileostomy.

Comparison of Magnetic Resonance Imaging and ^{13}C acetic-acid breath test for the assessment of gastric emptying

J.J.L. Haans[1], C.Y. Wong[1], J. Doornbos[2], A. de Roos[2], A.A.M. Masclee[1], Dept of Gastroenterology & Hepatology[1] and Radiology[2], Leiden University Medical Center, Leiden, The Netherlands

Several methods are currently employed to measure gastric emptying. In recent years Magnetic Resonance Imaging (MRI) has become available for human gastric motility studies, including gastric emptying measured through volume changes. The ^{13}C-acetic acid breath test is used especially in the clinical setting to evaluate gastric emptying. Aim of the present study was to compare gastric emptying as assessed by MRI and ^{13}C-acetic acid breath test during simultaneous recording. Ten healthy volunteers (8F; mean age 21 yrs; range 20-23 yrs) agreed to participate. Each volunteer consumed a 300 ml mixed liquid meal (450 kcal), labeled with a paramagnetic MRI contrast agent (750 µmol) and 150 mg ^{13}C-sodium acetate. After an overnight fast the meal was ingested and MRI volume scans covering the gastric region were obtained every 15 min for 120 min. Breath samples were collected at regular intervals from 0 to 240 min. Results are shown as mean ± SD. MRI volume scans showed a gastric meal volume of 358 ± 41 ml immediately after meal ingestion. Volumes decreased to 346 ± 28, 297 ± 40 and 100 ± 51 ml at 30, 60 and 120 min respectively. The ^{13}C-acetic acid breath test showed exhaled cumulative doses of 0.0 ± 0.0, 1.8 ± 0.3, 6.7 ± 0.9, 19.9 ± 2.8 and 37.8 ± 6.5 % at times 0, 30, 60, 120 and 240 min respectively. Overall sequential MRI volumes and ^{13}C-acetic acid cumulative doses showed excellent correlation ($r = -0.9$, $p<0.01$). However, half emptying time ($T_{1/2}$) obtained by MRI (91 ± 9 min) and ^{13}C-acetic acid breath test (134 ± 11 min) were significantly ($p<0.01$) different, with a delay in emptying as assessed by ^{13}C-acetic acid breath test. This delay results from methodological factors such as absorption, metabolic handling and excretion of the ^{13}C isotope. Conclusion: Gastric emptying curves obtained with MRI and ^{13}C-acetic acid breath test correlate perfectly. However individual time data, like half emptying time, cannot be used interchangeably due to methodological differences.

Regional Differences in Expression of SERT and TPH-1 in Patients with Gastroparesis and Healthy Controls

N. van Lelyveld, J. Ter Linde, M. Samsom. University Medical Centre Utrecht, The Netherlands

Serotonin (5-HT) plays an important role in gastric motor activity. Tryptophan hydroxylase (TpH) is the rate-limiting enzyme in the 5-HT biosynthetic pathway. The action of 5-HT is terminated through uptake by the serotonin transport protein (SERT). The aim of the study was to assess possible regional differences in serotonergic signalling by analysing SERT and TPH-1 expression in fundus and antrum of patients with gastroparesis and healthy controls. Methods: 7 female patients with gastroparesis (age 49.1 ± 4.6) and 8 female healthy controls (age 45.5 ± 3.3) participated in the study. All patients had delayed gastric emptying and were symptomatic at inclusion. Mucosal biopsy specimens of the antrum and fundus were obtained and immediately snap frozen during upper GI endoscopy. Expression analysis of SERT and TPH-1 was performed by quantitative real time RT-PCR. All cDNA samples were analysed in triplicate. The average was normalized against the endogenous reference gene porphobilinogen deaminase (PBGD). Ratios are given as a mean ± SEM. Results: PBGD was expressed at the same level in fundus and antrum. In all participants the expression of TPH-1 in the antrum was 1.2 ± 0.25 times higher compared to the fundus when normalized against PBGD. The expression of SERT was 30.9 ± 6.0 times higher in the antrum compared to the fundus. No differences in SERT or TPH-1 expression between patients and controls were found.
Conclusion: SERT and TPH1 expression in fundus and antrum is similar in patients with gastroparesis and controls. In all participants, the expression of TPH-1 in the antrum and the fundus is comparable. The production of serotonin is therefore likely to be comparable between the two regions. The expression of SERT is 30 times higher in antrum compared to fundus in all participants implying a higher capacity for serotonin uptake in the antrum. This regional difference may indicate either a higher release or a faster uptake of serotonin in the antrum.

Comparison of sensory perception and reproducibility of electrical mucosal stimulation (EMS) and rapid balloon distension (RBD) of the healthy human rectum

M.L. Harris[1], A. Hobson[1], S. Hamdy[1], D.G. Thompson[1], L.M.A. Akkermans[2], Q. Aziz[1]. Section of Gastrointestinal Science[1], University of Manchester, Hope Hospital, Manchester, UK and Gastrointestinal Research Unit, Dept of Surgery[2], University Medical Center Utrecht, The Netherlands

Patients with Irritable Bowel Syndrome often demonstrate abnormal rectal sensation. Currently, this is assessed by manual balloon distension or barostat. However, neither of these tests is adaptable for use in the neurophysiological characterisation of afferent pathways by cortical evoked potentials or magneto encephalography due to their slow onset time. We assessed the reproducibility, tolerance and type of sensation evoked by EMS and RBD. Eight healthy subjects (4F), median age 33 years, were studied on three separate occasions. Ano-rectal manometry was performed to ensure normal motor function. Rectal sensation was evoked using EMS with a constant current stimulator (0•5 Hz, 0-100 ma, 500 μs duration) and RBD with a rapid rate balloon pump inflator (0.5 Hz, 0-30 Psi, inflation cycle duration 250 ms). Intensities of rectal stimulation ranged from sensory threshold to maximum tolerated, in random order. Sensation was rated on visual analogue scales of pain, urge and unpleasantness. Both types of rectal stimulation were well tolerated by all subjects. Intra-class correlation coefficient for between occasions for EMS was 0.82 and RBD 0.72 demonstrating good reproducibility. However, both types of stimulation provoked different sensations. EMS invoked pain in all subjects. Comparatively, RBD rarely caused pain but in all cases provided a strong urge to defecate. All subjects reported significantly more unpleasantness during RBD than EMS ($P<0.01$). This study shows that EMS and RBD as tests of rectal sensory function are similarly reproducible. However, the sensations experienced with each technique varied markedly, probably reflecting differences in peripheral receptors stimulated or in the central processing of the sensory input. The two different quantitative ratings of sensation may be valuable in conjunction with novel neuroimaging techniques to provide insight into the neurophysiological characteristics of visceral afferent pathways in both health and disease.

Octreotide as potential treatment for patientswith non-constipated irritable bowel syndrome

T.K. Klooker, H. Beaumont, S.D. Kuiken, A. Lei, G.E. Boeckxstaens. Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands

Octreotide, a somatostatin analogue, inhibits afferent responses to rectal distention and possess an anti-hyperalgesic effect in irritable bowel syndrome (IBS). Whether prolonged treatment with octreotide also reduces visceral sensitivity and improves gastrointestinal symptoms remains however unknown. Therefore, we investigate the effect of a slow release preparation of octreotide on rectal sensitivity and symptoms in IBS patients. Forty two non-constipated IBS patients (19-63 yr, 20F) were invited to participate in this randomized, double blind, placebo-controlled, parallel group study. Before and after 8 weeks of treatment with octreotide (Sandostatine LAR 20 mg i.m. in week 1 and 5) or placebo, patients underwent a barostat study to assess rectal sensitivity using an intermittent pressure-controlled and a slow ramp volume-controlled distention protocol. During a 2 week run-in period and during treatment, abdominal pain, defecation frequency, consistency and symptom relief were scored every week. Octreotide, but not placebo, significantly increased the threshold for first sensation (before: 1.9±0.3 mmHg; after: 3.4±0.4 mmHg, $P<0.005$; Wilcoxon Signed Ranks test). Thresholds for urge to defecate and discomfort/pain and rectal compliance were not altered by either treatment. During octreotide, more patients reported improvement of abdominal complaints (mean % over the 8 weeks: octreotide: 35±2%, placebo: 26±3%, $P<0.05$; Mann-Whitney U test) compared to placebo. Furthermore, octreotide improved stool consistency compared to placebo (loose and watery stools: octreotide: 49±3%, placebo: 64±2% $P<0.01$). In contrast, abdominal pain and defecation frequency were not affected.
Conclusions: This study shows that treatment with octreotide reduces the threshold for first perception confirming its visceral analgesic effect. In addition, octreotide reduces abdominal complaints and improves stool consistency, suggesting that octreotide may be beneficial in non-constipated IBS.

Gastric hypersensitivity induced by esophageal acid infusion in healthy volunteers

B.D. van den Elzen[1], G.N. Tytgat[1], G.E. Boeckxstaens[1], Dept of Gastroenterology[1], Academic Medical Center Amsterdam, The Netherlands

Visceral hypersensitivity plays an important role in the pathogenesis of functional dyspepsia. We hypothesized that distal esophageal acid exposure could induce visceral hypersensitivity of the stomach. 18 HV (13f; 22 y (18–36)) underwent a gastric barostat combined with acid or saline infusion in the distal esophagus. In 8 HV the infused liquid was recovered at the lower esophageal sphincter. Gastric sensitivity was assessed by a limited randomized phasic distensions (4,7,10,13 mm Hg above MDP) before and every 30 min up to 2h after the start of a 30-min infusion period with HCl 0.15 M or saline. Duodenal pH was continuously monitored. Dyspeptic symptoms were scored on a visual analogue scale during each distension. A Wilcoxon signed rank test was used for statistical analysis. Directly after acid infusion, but not after saline, the threshold for discomfort decreased significantly (5.9 ± 2.0 vs. 12.3 ± 0.5) and bloating (250 ± 38 vs. 156 ± 30 mm), nausea (246 ± 41 vs. 121 ± 35 mm), pain (151 ± 47 vs. 78 ± 39 mm) and epigastric burning (60 ± 16 vs. 10 ± 3 mm) were significantly increased at 30 min compared to baseline ($p<0.05$). These symptoms declined over 120 min. In 2 HV, sensitivity to distension was significantly increased without acidification of the duodenum. In contrast, when the infused liquid was recovered, the effect of acid infusion on gastric sensitivity was abolished (10.4 ± 0.8 vs. 12.6 ± 0.4;ns) and the increase in bloating (218 ± 9 vs. 177 ± 11 mm; $p<0.05$), nausea (165 ± 46 vs. 98 ± 30 mm; $p< 0.05$), pain (85 ± 32 vs. 49 ± 15 mm; ns) and epigastric burning (100 ± 39 vs. 31 ± 17 mm; ns) at 30 min was reduced returning to baseline at 60 min.
Conclusion: Distal esophageal acid infusion even in the absence of duodenal acidification induces visceral hypersensitivity leading to dyspeptic symptoms in HV. As reduction of the acid load to the stomach prevented this effect, our findings indicate that gastric rather than esophageal acidification is involved.

Molecular typing methods show different fingerprints for the faecal bacterial composition in irritable bowel syndrome (IBS) patients and healthy subjects.

A.P.M. Kerckhoffs[1], M. Samsom[1], G.P. van Berge Henegouwen[1], A.J.P.M. Smout[1], M. van der Rest[2], J. Knol[3], E.A.F. van Tol[3], L.M.A. Akkermans[1]. Depts of Gastroenterology and Surgery[1], Gastrointestinal Research Unit, University Medical Center Utrecht, Microscreen[2], Groningen and Numico Research BV[3], Wageningen, The Netherlands

Faeces of IBS patients contain higher numbers of facultative anaerobic bacteria and low numbers of lactobacilli and bifidobacteria compared to healthy subjects. The detection and identification of bacteria by culturing is often hampered by the limitations of culture conditions and a large number of intestinal bacteria cannot be cultured. Molecular methodologies using ribosomal RNA enable a more complete and accurate quantification of the most dominant groups of faecal bacteria. We investigated differences in the faecal flora between 18 IBS patients and 20 healthy subjects using molecular biological methods. Total bacterial DNA was determined using quantitative polymerase chain reaction (PCR). The bacterial 16S rRNA gene was amplified and analysed using denaturing gradient gel electrophoresis (DGGE) and the average DGGE profiles of IBS patients and healthy controls were compared. Using quantitative PCR the total bacterial load was determined to be 10^{11} bacteria per gram faeces in both groups.Comparing the average fingerprints of both groups 85% of the bands were identical and 32 bands were unique for healthy subjects and 23 bands were unique for IBS patients, revealing a difference in the diversity of the bacteria in faecal samples. A dominant unique band that may still represent multiple species was identified in healthy subjects. Although the quantity of bacteria in faecal samples of IBS patients and healthy controls is similar the molecular fingerprints indicate distinct differences of the intestinal bacteria of IBS patients and healthy subjects. Analyses of the differences between IBS patients and healthy subjects by averaging the DGGE profile have not been used before. This approach reveals that 85% of the profiles are identical and 55 bands appear to be unique. The healthy subjects contain a very distinct and dominant band, which is not present in the IBS patients. Differentiating bands will be further evaluated to identify specific bacterial populations.

Adults with corrected oesophageal atresia (OA): Are complaints predictive of oesophageal function and/or quality of life (QoL)?

J.A. Deurloo[1], E.C. Klinkenberg[2], S. Ekkelkamp[1], H.A. Heij[1], D.C. Aronson[1]. Pediatric Surgical Center[1], Amsterdam (Emma Children's Hospital/AMC and Vrije Universiteit Medical Center), Dept of Gastro-enterology[2], VU University Medical Center, Amsterdam, The Netherlands

The aim of this study was to evaluate oesophageal function after correction of OA in adults, and to investigate the correlation between complaints, oesophageal function and QoL.
We included 60 patients (>18 years old) who participated in previous follow-up studies, in which complaints of dysphagia and gastro-oesophageal reflux (GOR) were registered and results of upper GI endoscopy, oesophageal biopsies and QoL (SF-36 + GIQLI) had been collected. 25/60 patients agreed to undergo manometry and 24-hour pH-measurements, which were successful in 20 patients. Manometry was performed using a catheter with 3 pressure transducers at 5 cm distance. The pH-probe was positioned 5 and 20 cm above the upper border of the lower oesophageal sphincter (LOS). pH-values (sample time 5 seconds) were calculated using criteria of Johnson and Demeester. Correlations were tested with ANOVA and χ^2-tests.
Ten patients (50%) reported complaints of dysphagia, 7 (35%) of GOR. Mean LOS pressure: 13.1 ± 7.2 mm Hg; sphincter relaxation was complete in all patients. The amplitude of oesophageal contractions was normal (> 35 mmHg) in 6 (30%), moderate (15-35 mmHg) in 10 (50%), and low (<15 mmHg) in 4 (20%). Oesophageal motility was non-specifically disturbed in 19 patients (95%). pH-measurements showed a normal pattern in 16 (80%), minor reflux in 1 (5%), and pathological reflux in 3 (15%). Patients reporting dysphagia more often had disturbed motility (p=0.011), and lower scores on the domains 'general health perceptions' (SF-36)(p=0.043) and 'standardised physical component' (SF-36) (p=0.022). No other correlations were found between complaints, functional results and QoL.
This study shows a high percentage of oesophageal motility disturbances and a moderate percentage of GOR after correction of OA. Patients reporting dysphagia more often had disturbed motility and had lower scores on some domains of the SF-36. No other correlations were found between complaints, functional results and QoL.

Early events in antigen-specific CD25neg TR cell induction via the mucosa. (Final report Maag Lever Darm Stichting project no. MWO 02-68)

F. Hauet-Broere, L. van Berkel, W. Unger, G. Kraal, J. Samsom. Dept of Molecular Cell Biology and Immunology, VU University Medical Center, Amsterdam, The Netherlands

In mice, oral or nasal application of OVA leads to antigen specific suppression of both DTH and IgE responses. This tolerance can be transferred to naive recipients by $CD4^+$ regulatory T cells (T_R) from the spleen. These mucosal T_R function irrespective of cytokine polarization and exert systemic suppression through "infectious" tolerance by passing their tolerizing capacity on to naive T cells. Phenotypic analysis of these $CD4^+$ T_R revealed that they are present in both $CD25^+$ and $CD25^-$ T cell subsets, although, in contrast to the $CD25^+$ T cell subset, suppression by the $CD25^-$ T_R population is antigen-specific. To unravel where naive $CD4^+$ T cells differentiate into these specialized antigen specific $CD25^-$ T_R during oral and nasal tolerance, we followed the fate of transferred OVA T-cell-receptor transgenic DO11.10 cells in vivo. We demonstrate that within 48 h after mucosal OVA application, $CD4^+$ DO11.10 T cells divide in the mucosa draining LN, but not in peripheral LN. Similarly, non-mucosal (i.m.) OVA application induced $CD4^+$ DO11.10 T cells to proliferate in the draining inguinal LN (ILN), albeit more vigorously and with different kinetics. Even though this differentiation of T_R and effector T cells exhibited striking similarities, functional analysis revealed that only proliferating $CD4^+$ DO11.10 T cells from mucosa draining LN, and not ILN, could transfer tolerance to naive recipients. Further phenotypic and functional analysis of these cells is currently being performed. Specific interference in mucosal homeostasis by inhibiting cyclooxygenase-2 derived arachidonic acid metabolites during OVA feed enhanced DC migration and IL-12 secretion in the mucosa draining LN and may explain an observed aberrant Tr differentiation and concomitant loss of oral tolerance. Defective Tr formation was not associated with altered kinetics of DO11.10 division, but was accompanied by an increased IL-4 release. Neutralizing this IL-4 proved to be sufficient to restore tolerance. These data provide insight into both the induction of highly discriminative mucosal T_R as well as their broad down-regulatory activity.

Genotypic and phenotypic differences between pediatric/adolescent-onset and adult-onset IBD.

L. de Ridder[1], P.C.F. Stokkers[2], I. Pronk[3], M.A. Benninga[1], J.A.J.M. Taminiau[1], D.W.Hommes[2]. Dept of Pediatric Gastroenterology[1], Emma Children's Hospital, Academic Medical Center, Amsterdam, Dept of Gastroenterology[2] and Lab of Exerimental Internal Medicine[3], Academic Medical Center, Amsterdam, The Netherlands

Genetic susceptibility probably plays a more important role in early-, than in late-onset IBD. If so, a higher frequency of the NOD2/CARD15 gene mutation can be expected in pediatric CD patients. We determined the frequency of the 3 major NOD 2/CARD15 and 2 TLR 4 mutations in a Dutch pediatric IBD cohort. Thereby, genotype and phenotype of pediatric and adult onset IBD were compared.Genomic DNA from 62 pediatric IBD patients (45 CD, 16 UC, 1 indeterminate) and 472 adolescent CD patients was screened for the R702W, G908R and 1007fs loci of NOD2/CARD15 gene. The Asp299Gly and Thr399Ile polymorphisms in TLR4 were assessed for the pediatric cohort and an adult cohort of 407 CD patients and 226 UC patients. The screening was accomplished by a PCR and restriction fragment-length polymorphism assay, with specific primers and restriction enzymes for each polymorphism. Phenotypic data were assessed.In the pediatric CD cohort 56,8% had ileal disease localization versus 63,3% of the adult CD patients. Colonic involvement was seen in 68,2% of the pediatric CD patients and in 37,9% of the adults. In the pediatric cohort carriage of two mutated alleles was associated with ileal disease ($c2=6.3$, $p=0.012$). Homozygosity for the 1007fs mutation was noted in 6,5% of the pediatric cohort whereas 0,4% of the adult patients were homozygous ($c2=16,1$ $p<0.0004$). Three patients of the pediatric cohort (6,5%) were compound heterozygote compared to 20 adult CD patients (4,2%). In total 7 (15,5%) pediatric CD patients and 36 adult CD patients (7,6%) were either compound heterozygous or homozygous for NOD2/CARD15 mutations. Three out of 16 pediatric UC patients were heterozygous for the two TLR4 polymorphisms versus 25 of the 226 adult UC patients tested. These differences were not statistically significant.We observed a higher frequency of the CD related genotypes in the pediatric cohort, although this finding was statistically significant only for the 1007fs mutation.

The Toll-like receptor 4 (TLR4) Asp299Gly polymorphism isassociated with colonic localization of Crohn's disease, without a major rolefor the Saccharomyces cerevisiae mannan-LBP-CD14-TLR4 pathway

R. Mallant-Hent, S. Ouburg, J.B.A. Crusius, A.A. van Bodegraven, C.J.J. Mulder, R. Linskens, A.S. Peña, S.A. Morré. Lab of Immunogenetics and Dept of Gastroenterology, VU University Medical Center, Amsterdam, The Netherlands

In recent literature a novel association of the Toll-like receptor 4 (TLR4) +896 A>G polymorphism with both Crohn's disease (CD) and Ulcerative colitis (UC) has been described, supporting the genetic influence of pattern recognition receptors (PRRs) in triggering inflammatory bowel disease (IBD). The aim of our study is to investigate the *TLR4+ 896* A>G and *CD14 -260* C>T polymorphisms and to relate these results to ASCA status and Vienna Classification. Our study group consisted of 112 CD patients, 101 UC patients and 170 unrelated Dutch Caucasian controls (HC). The *CD14 -260* and *TLR4 +896* genotypes, allele, and carrier frequencies were compared between the different clinical patient groups and controls. In addition, synergism between *CD14* and *TLR4* genotypes and alleles (carrier trait analyses) were studied. The frequency of the G allele of *TLR4+896* was significantly increased in CD patients compared to UC patients and HC (19% vs.11% vs. 10%; CD vs. HC p: 0.049; OR 2.1 [95% CI: 1.0-4.1]). Carriage of *TLR4 +896**G significantly increases the risk for colonic localization of CD compared to non-colonic localization (43% vs. 12%; p: 0.0017; OR: 5.5 [95% CI: 1.9 – 15.4]). There was a clear trend (Test for trend: Chi-square: 16, p<0.0001) when we compared the increasing frequency of the G allele of *TLR4 +896* in controls (10%) to CD patients (19%) to CD patients with a colonic localization (43%). A trend towards younger age (A1) could be observed for the carriage of the *TLR4* G allele, though this did not reach statistical significance. Univariant analyses showed that the mutations in CARD15 are not confounding for the found associations with TLR4. Multivariant analyses for confounding factors are in progress. There was no difference between *TLR4* G allele carriage in the ASCA positive and ASCA negative patients (23% vs. 14%; p: 0.33) and there was no difference between *TLR4* G allele carriage in the ASCA positive and negative CD patients with colonic localization (40% vs 46%; p: 1.00), while the frequency of G allele carriage was identical to that of CD patients with colonic localization (43%) without correcting for the ASCA status. The association we demonstrate between TLR4 and CD is most likely not strongly based on the *S. cerevisiae* mannan-LBP-CD14-TLR4 pathway, as we have shown based on the ASCA data in our group.

PCR results of Saccaromyces cerevisiae in intestinal mucosal samples of patients with IBD

R.C. Mallant-Hent[1], M. Mooij[2], R.K. Linskens[4], B.M.E. von Blomberg[3], A.A. van Bodegraven[1], P.H.M. Savelkoul[2]. Dept of Gastroenterology[1] and Medical Microbiology, VU University Medical Centre, Amsterdam, Dept of Gastroenterology, St.Anna Hospital, Geldrop, The Netherlands

Introduction: Anti-Saccharomyces cerevisiae antibodies (ASCA) are known to be positive in about 65% of Crohn's disease (CD) patients and are currently used to subtype the disease in different phenotypes. More precisely, ASCA has been associated with small bowel disease, fibrostenosis, internal perforations and small bowel surgery. The cause of ASCA formation/generation is still unknown. Some authors have considered antibody formation as a consequence of increased mucosal permeability.We investigated the correlation between ASCA and presence of mucosal S. cerevisiae in a population of CD and ulcerative colitis (UC) patients. We designed S. cerevisiae specific primers and a fluorescent probe for a 5'exonuclease (TaqManTM) assay. This assay is a homogenous system using a fluorescent labeled probe for the detection of PCR product in 'real time'. We related the PCR results with the ASCA findings in a group of 67 IBD patients (31 CD, 45 UC) and 22 healthy controls (HC). Results: ASCA (IgA or IgG) were positive in 18 CD (58%), 11 UC (24%) and none of the HC.Technical problems with DNA extraction and amplification occurred in 10 UC patients (22%), 7 CD patients (22%) and 6 HC (30%). In only 10 of the mucosal samples S. cerevisiae could be demonstrated by TaqMan: 4 in CD (13%), 5 in UC (11%), 1 in HC (5%).In 2 CD patients both ASCA IgA and IgG and mucosal S. cerevisiae were positive. In 3 UC patients both ASCA IgG and mucosal S. cerevisiae were positive. In one UC and two CD patient mucosal S. cerevisiae was present in combination with negative ASCA IgA and IgG. Conclusion: In this study ASCA positivity in the UC group was very high, probably due to selection bias, since only patients undergoing endoscopy for clinical reasons were included in the study. However, we conclude that since the presence of S. cerevisiae in mucosal biopsies is very rare, ASCA can not be explained by continuous exposure to S. cerevisiae. Therefore ASCA formation must be initiated earlier in life and levels remain relatively stable thereafter as has been documented in literature before.

Maintenance treatment with 6-thioguanine in azathioprine or 6-mercaptopurine intolerant inflammatory bowel disease patients

N.K.H. de Boer[1], L.J.J. Derijks[2], L.P.L. Gilissen [3], D.W. Hommes [4], L.G.J.B. Engels[5], S.Y. de Boer[6], G. den Hartog[6], P.M. Hooymans[7], A. Makelburg[8], A.H.J. Naber[9], B.D. Westerveld[8], C.J.J. Mulder[1], D.J. de Jong[9]. Depts of Gastroenterology & Hepatology: VU University Medical Centre Amsterdam[1], Academic Hospital Maastricht[3], Academic Medical Center Amsterdam[4], Maasland Hospital Sittard[5], Rijnstate Hospital Arnhem[6], Isala Clinics Zwolle[8], Radboud University Nijmegen Medical Centre[9] and Depts of Clinical Pharmacy: Maxima Medical Centre Veldhoven[2] and Maasland Hospital Sittard[7], The Netherlands

Up to 30% of patients with inflammatory bowel disease (IBD) is intolerant to azathioprine (AZA) or 6-mercaptopurine (6MP) treatment. By administering 6-thioguanine (6TG), which is almost directly converted to the pharmacologically active 6-thioguaninenucleotides (6TGN), toxic pathways are possibly avoided. The aim of our study was to determine the tolerability and safety of a low-dose maintenance therapy with 6TG in AZA or 6MP intolerant IBD patients over a treatment period of at least one year by a database analysis. 20 out of 95 (21%) patients discontinued 6TG use within 1 year. Main reasons for discontinuation were GI-complaints (31%), general malaise (15%) and hepatotoxicity (15%). Haematological events occurred in 3 patients (discontinuation in 1). In the 6TG tolerant group 9% (7/75) could be classified as hepatotoxicity on 6TG (defined as 1 liver test above 2xUNL) at one year use. Two of these patients had elevated liver tests before the start of 6TG, 1 patient had a choledocholithiasis (ultrasound), 2 patients had a single liver test elevation (GGT) without clinical complaints, one patient (306 days 20 mg 6TG) had a splenomegaly and a gallbladder hydrops with sludge and the last patient underwent a liver biopsy that showed steatosis. An abdominal ultrasound was performed in 54% of patients after 1 year. Five ultrasounds were considered as abnormal: steatosis (N=3) and the 2 described above. The mean 6TG dose was 24 mg daily with a mean 6TGN level of 540 pmoles/8x10 RBC. A global physician score (GPS) was determined in 85% of the tolerant patients at 1 year; 73% was classified as better and 6% as worse. Conclusion: The majority of AZA or 6MP intolerant IBD patients (79%) tolerates maintenance treatment with 6TG (dosed 0.3-0.4 mg/kg/daily). The use of 6TG may still be considered as an escape immunosuppressant in this group of patients. However, the reported hepatotoxicity is worrisome. 6TG should therefore only be administered in clinical trials

Long-term results of intravenous cyclosporine in steroid-resistant ulcerative colitis

A.B.U. Mäkelburg[1], F.G.A. Jansman[2], J. Vecht[1], B.D. Westerveld[1]. Depts of Gastroenterology[1] and Clinical Pharmacology[2], Isala klinieken, Zwolle, The Netherlands

Two reports exist on the long-term efficacy of intravenous cyclosporine-therapy in patients with steroid-resistant ulcerative colitis (UC). These studies have been performed in tertiary referral-centers. We report the results in a non-referral large regional hospital.All patients with UC treated in our clinic with cyclosporine A (CSA) i.v. in the years 1994-2004 were identified. Patients were treated according to a standard protocol including 4mg/kg CSA and 40mg of prednisone. Azathioprine was discontinued. The charts were reviewed with attention to colectomies, complications and survival.In our study 61 patients were included. Follow-up varied from 7-124 months (median 57.4 months). A colectomy was performed in 32 patients (52.5%): 15 acute (< 4 weeks) and 9 semi-acute (4-13 weeks) and 8 after 13 weeks. Five patients were treated twice with CSA i.v.: four of them underwent colectomy. The median interval from the start of CSA therapy to colectomy was 2.4 months (range 2 days – 57 months). No deaths or major adverse events were encountered during CSA therapy. Five patients required antihypertensive therapy; one patient was admitted with a CMV-infection six weeks after discontinuation of therapy. Two patients died during follow-up: one patient died in the postoperative phase after colectomy, another patient died four years after initial CSA-therapy in another hospital due to a toxic megacolon.
Conclusions: Intravenous CSA in patients with severe UC proved to be safe in our setting. In 47% of the patients a colectomy could be prevented.References:1) Cohen RD, Stein R, Hanauer SB. Intravenous cyclosporine in ulcerative colitis: A five-year experience. Am J Gastro-enterol 1999;94:1587-15922) Arts J, D'Haens G, et al. Long-term outcome of treatment with intravenous cyclosporine in patients with severe ulcerative colitis. Inflamm Bowel Dis 2004;10:73-78

Autologous Hematopoietic Stem Cell Transplantation for Severe Refractory Crohn`s Disease

Z. Zelinkova[1], M-J. Kersten[3], I. Pronk[1], K. Horsthuis[4], R. van Oers[3], S. Lange[2], D. Hommes[2]. Lab of Experimental Internal Medicine[1] and Depts of Gastroenterology[2], Clinical Hematology[3] and Radiology[4], Academic Medical Centre, Amsterdam, The Netherlands

Recently, a few cases have been reported on successful remission induction of patients with therapy-resistant Crohn`s disease (CD) by means of allogeneic- or autologous hematopoietic stem cell transplantation (HSCT). The beneficial effects of immune reconstitution and repopulation of immune cells are not yet elucidated in these patients. We report on the first transplanted patient in the Netherlands.
Autologous HSCT was offered to a 51-year old male with objectively diagnosed Crohn's disease of almost the entire small bowel. He failed to respond to steroids in combination with azathioprine/methotrexate and infliximab. Surgery would have put him at great risk of developing a short bowel syndrome. The mobilisation phase included cyclophosphamide 4g/m2 and G-CSF 2dd 5µg/kg. Prior to transplantation, immune ablation was achieved using cyclophosphamide 50mg/kg/day (4 days), ATG 30mg/kg/day (3 days) and prednisolon 500mg (3 days). Endoscopy and both barium- and MRI-enteroclysis was performed at baseline and 3 months. Activation markers, homing and chemokine receptors were assessed during the mobilization and follow-up after HSCT in the repopulating peripheral blood mononuclear cells.
Although an initial clinical response after mobilization was observed, he suffered from a rapid clinical- and endoscopic relapse within weeks. During the HSCT patient developed an allergic reaction to ATG that resolved with a standard treatment and the HSCT was completed successfully. In week 8 of the follow-up after HSCT, the patient was clinically in complete remission, gaining weight and without need for a supplementary parenteral nutrition. Endoscopically, a clear improvement of the inflammatory lesions was observed. As expected, residual strictures persisted. No significant changes have been observed in the studied markers on peripheral blood mononuclear cells during the follow-up.
Autologous HSCT seems to be an alternative strategy for CD patients with severe and therapy resistant disease.

FDG-PET detects clinical relevant adenomas of the colon: a prospective study of 100 patients

M.C.A. van Kouwen[1], F.M. Nagengast[1], J.B.M.J. Jansen[1], W.J.G. Oyen[2], J.P.H. Drenth[1]. Depts of Gastroenterology and Hepatology[1] and Nuclear Medicine[2], Radboud University Nijmegen, Medical Centre, The Netherlands. Both W.J.G. Oyen and J.P.H. Drenth qualify as last authors.

2-(18F)-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) is a non-invasive imaging technique clinically used to detect malignant tumors. FDG-PET has been established as a tool for diagnosis of recurrent or metastatic colorectal carcinoma. Several case series suggest that FDG-PET also detects larger adenomas. To set out to investigate whether FDG-PET is able to detect colonic adenomas.FDG-PET was performed in 100 consecutive patients in whom colonic adenomas were suspected on barium enema (n=47) or sigmoidoscopy (n=53). A positive scan was defined as focal large bowel FDG accumulation. FDG-PET was followed in all cases by colonoscopy, and removed adenomas were examined histopathologically. Colonoscopy confirmed the presence of adenomas in 68/100 patients. In 35 there was focal FDG accumulation at the site of the adenoma, especially in larger adenomas (> 15 mm) (80%) or in adenomas with severe dysplasia (86%). FDG accumulation was absent in 33 patients with adenomas, and in general those adenomas were small and/or showed only mild dysplastic changes.In conclusion, FDG-PET detects 81% of the adenomas with high-grade dysplasia or carcinoma and 80% of the adenomas > 15 mm. The grade of dysplasia is the most important discriminative factor that predicts detection by FDG-PET. The direct clinical implication of our study is that focal colonic FDG accumulation has to be followed by colonoscopy and subsequent polypectomy.

Heterozygous polymorphisms in the genes encoding ITPA and TPMT*3A are not predictive for the development of adverse effects of Azathioprine treatment in IBD patients

J.M. van Dieren[1], A.J. van Vuuren[1], E.J. Kuipers[1], J.G. Kusters[1], E.E. Nieuwenhuis[2], C.J. van der Woude[1]. Depts of Gastroenterology & Hepatology[1] and Pediatric Gastroenterology[2] Erasmus MC, University Medical Center Rotterdam, The Netherlands

Azathioprine (AZA), an effective treatment of IBD, is associated with adverse events, including hepatotoxicity and leucopenia. The inactivation of 6-MP, the active metabolite of AZA, involves the enzymes thiopurine S-methyltransferase and inosine triphosphate pyrophosphatase. It has been suggested that patients with polymorphisms in genes encoding these enzymes (TPMT and ITPA respectively) are at higher risk for adverse effects. The aim of this study was to determine whether the detection of polymorphisms in ITPA and TPMT are of extra value for the prediction of adverse effects in AZA therapy. Off all 96 IBD patients, both children and adults, who started AZA therapy in our clinic between January 2003 and November 2004, side effects were documented and TPMT and ITPA genotypes were determined by PCR. 21 (22%) had 22 polymorphisms; 11 heterozygous ITPA alleles, 10 heterozygous TPMT alleles (8 type 3A, 1 type 3B and 1 type 3C) and 1 homozygous TPMT polymorphism (type 3A). One exhibited both a heterozygous TPMT*3A and ITPA allele. Heterozygosity for the ITPA or TPMT*3A allele was associated with a low frequency of adverse effects (1/8 vs. 2/11 respectively). Also, no adverse effects were documented for the patient with the coincidental ITPA/TPMT*3A polymorphism. Patients with other TPMT polymorphisms mentioned (3B, 3C or homozygous 3A), all presented with adverse effects (1/1 leucopenia, 1/1 hypersensitivity, 1/1 pancytopenia respectively). Wildtype patients also exhibited adverse effects (27/75) (6/21 vs. 27/75 wildtype, p=0,5). Leucopenia occurred in 0/11 with the ITPA- and in 1/8 with the TPMT*3A allele vs. 6/75 in wildtype patients (TPMT*3A and ITPA polymorphisms vs. wildtype, p=0,7). Hepatotoxicity occurred in 1/11 with the ITPA- and 0/8 in the TPMT*3A allele-group vs. 7/75 in wildtype patients (p=0,6). In conclusion, heterozygosity for a TPMT*3A or/ and an ITPA polymorphism is not predictive for the development of adverse effects of AZA.

The severity of steatosis effects liver regeneration in a rat model

R. Vetelaïnen, A.K. van Vliet, T.M. van Gulik. Dept of Surgery (Surgical laboratory), Academic Medical Center Amsterdam, The Netherlands

Steatosis impairs liver regeneration but the effect of the severity of steatosis and steatohepatitis on liver regeneration remains unclear. We assessed the effect of microvesicular steatosis and macrovesicular steatosis with mild inflammatory activity on liver regeneration after 70% hepatectomy.Methione and choline deficient diet (MCDD) was used to induce steatosis and steatohepatitis 1 and 5 weeks, respectively. Wistar rats (300-325g) were divided into three groups (n=5): MCDD one week, MCDD 5 weeks and normal diet. Steatosis and steatohepatitis was evaluated by liver triglycerides content and histopathology. After 70 % hepatectomy rats were sacrificed at 24, 48 and 72 h. Liver regeneration (MIB-5 proliferation and mitotic indexes and regenerating liver mass), hepatocellular injury (AST, ALT, bilirubin), the proinflammatory cytokine response (TNF-α, IL-1β, IL-6), apoptosis (caspase-3 index) and liver histo-pathology were assessed. MCD diet induced steatosis after one (<30% hepatocytes, microvesicular steatosis) and steatohepatitis after 5 weeks (>60% hepatocytes, macrovesicular steatosis, inflammatory activity, mild fibrosis) confirmed by histology. After 70% hepatectomy, the regenerated liver mass was lowest in steatohepatitis group compared to steatosis and control groups at 24h, 48h and 72 h ($p<0.05$). Both the MIB-5 and mitotic indexes were lowest at 48h and 72h compared to steatotic and control groups ($p<0.05$). Also AST, ALT and bilirubin levels were higher in steatohepatitis group at all time points ($p<0.05$). TNF-alpha, IL-1beta, IL-6 were significantly higher in steatohepatitis group ($p<0.05$) and percentage of apoptotic hepatocytes stayed increased at 72h compared to control and steatosis groups ($p<0.05$).The presence of inflammation together with macrovesicular steatosis impaired liver regeneration and increased liver injury after hepatectomy suggesting increased risk when performing extensive resection in presence of steatohepatitis.

Direct and synergistic inhibition of hepatitis C virus replication by cyclosporin a and myocophenolic acid

L.J.W. van der Laan[1], S.D. Henry[1], R. Bartenschlager[3], H.W. Tilanus[1], H.J. Metselaar[2]. Depts of Surgery[1] and Gastroenterology & Hepatology[2], Erasmus MC-University Medical Center, Rotterdam, The Netherlands and Dept of Molecular Virology[3], University of Heidelberg, Germany

Background: Chronic Hepatitis C Virus (HCV) infection is the leading indication for liver transplantation worldwide. The success of transplantation is compromised by the re-infection of the graft and this problem seem to have worsened in the last decade. Changes in immunosuppressive therapy may have contributed for this deterioration. The aim of this study is to determine the direct effect of different immunosuppressive compounds on HCV replication.
Methods: The anti-viral properties of immunosuppressive drugs were tested in vitro using an HCV-replication model containing a luciferase reporter gene. HCV replication was quantified by luciferase activity and the detection of viral mRNA and RNA-polymerase (NS5B) protein expression.
Results: HCV replication was almost completely inhibited by pegylated IFN-α 2.5 IU/ml; 98.6% ± 0.3 SEM). Both cyclosporin A (CsA; 0.5-2.0 µg/ml) and mycophenolic acid (MPA; 2.0-6.0 µg/ml) blocked HCV replication up to 70 %. A significant synergistic inhibition was observed when CsA and MPA were combined, reaching maximum inhibition of 88 % ± 2 SEM at higher doses. The anti-viral kinetics of CsA and MPA were different. Inhibition was already observed after two hour incubation with CsA, but not with MPA. Both CsA and MPA did not induce cell death at any concentration. Proliferation of Huh-7 cells was reduced to some extent by MPA, but this did not account for the observed inhibition of HCV replication. No specific inhibitory effect was observed with tacrolimus (50-500 ng/ml), dexamethason (0.5-2.0 nM) or prednisolon (0.5-5.0 nM).
Conclusion: The immunosuppressive drugs CsA and MPA both are potent and specific inhibitors of HCV replication. The synergy and different anti-viral kinetics suggest that both drugs act via independent pathways. Immunosuppressive therapy based on a combination of CsA and MPA could be beneficial to reduce HCV recurrence after transplantation and boost conventional anti-viral therapy in chronic patients.

TIPS outcome and its determinants

E. Bos[1], V. Williams[2], E. van der Linden[2], B. van Hoek[1]. Dept of Gastro-enterology and Hepatology[1], and Dept of Radiology[2], Leiden University Medical Center, The Netherlands

In order to further improve results of transjugular intrahepatic porto-systemic shunt (TIPS) we analyzed outcome at 1, 3 and 12 months. and its determinants.
Methods: 1/1993-1/2004 93/96 (97%) of consecutive TIPS succesfull, 57 for variceal bleeding (V), 30 for refractory ascites (A, incl 1 hydrothorax), 5 for Budd-Chiari syndrome (BCS), 1 for hepatopulmonary syndrome. Uncovered stent before, covered after 11/2000. Child-Pugh (CP) classes A in 9, B in 46, C in 36, MELDscore was ≤17 in 69, >17 in 20. Follow-up until 1/2005 or death or liver transplantation (LT). Half-yearly Doppler, yearly angiography, re-intervention if needed. Patency and LT-free patient survival (SURV) (Kaplan-Meier, log-rank), cause of death and compli-cations assessed, predictors of survival by univariate and multivariate regression. Results: SURV at 1, 3,12 months 78%, 72%, 56%; for CP A 89%, 89%, 89%, in CP B 91%, 89%, 69%, for CP C 60%, 47%, 33% (p=0.0001), for MELD ≤17 85%, 81%, 64%, for MELD>17 55%, 44%, 29% (p=0.0007). SURV after acute TIPS (65%, 55%, 49%) similar to elective TIPS: 82%, 77%, 58% (p=0.13). SURV after TIPS for V (77%,71%, 62%) similar to that for A (76%, 68%, 39%)(p=0.22). For BCS, only the one with MELD>17 needed LT. Wall- vs Viatorr stents at 1, 3 and 12 months: primary patency 81%, 79%, 54% vs 90%, 90%, 86% (p=0.0169), primary assisted patency 85%, 80%, 75% vs 97%, 97%, 87% (p=0.0147), secondary patency 95%, 91%, 84% vs 97%, 97%, 87% (p=0.0236). HE in 48 patients (52%) post TIPS, in 16 (17%) new. Other complications in 36, 1 fatal. 9/57 (16%) rebled after TIPS for V due to sclerosingulcer, shunt dysfunction or liver failure. After 10/30 (33%) TIPS for A it remained refractory. Pre-TIPS multivariate predictors of 1-year survival: serum albumin, bilirubin, creatinin, PT/INR, thrombocyte count, age, gender, encephalopathy.
Conclusions: Excellent patency with covered stents, less with uncovered stents despite more interventions. Survival is related to liver function but not to acuteness or indication.

Polytetrafluoroethylene (ePTFE) Covered and Uncovered Stents for TIPS in Budd-Chiari Syndrome: a Single Center Experience

S. Darwish Murad[1], P.M.T. Pattynama[2], H.R. van Buuren[1], S.J.G.C Frerichs[2], H.L.A. Janssen[1]. Depts of Gastroenterology & Hepatology[1] and Radiology[2], Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands

Transjugular intrahepatic portosystemic shunt (TIPS) is an accepted therapy in patients with Budd-Chiari Syndrome (BCS). However, the main drawback of TIPS using conventional, uncovered stents is the high rate of shunt dysfunction (40-60%). The introduction of the polytetrafluoroethylene (ePTFE) covered stent has resulted in increased TIPS-patency in cirrhosis-induced portal hypertension, but little is known on the outcome in BCS, often associated with underlying hypercoagulability. The aim of the present single-center study was to evaluate the outcome of covered and uncovered TIPS in a consecutive series of recent diagnosed patients with BCS.Radiological diagnosis was made between January 1994 and December 2003. Patients underwent angiography and/or Doppler ultrasound examination to evaluate shunt patency at week 1, month 3, 6, 9 and 12 and every 6 months after TIPS.Twelve patients (8 female, median age 29.3 years) underwent TIPS 2.3 months after diagnosis (median; range: 0-94). Indications were refractory ascites (n=10) and liver failure (n=2). All patients received anticoagulation. TIPS placement was technically successful in all cases and no major complications occurred. Median follow-up was 2.2 years (0.2-8.2). A total of 14 uncovered and 15 covered stents were inserted. The 1-year primary patency rate was 67% (95% CI 14-100%) for the covered stents and 14% (95% CI 0–39%) for the uncovered stents (p=0.08). The primary assisted patency (i.e. irrespective of reintervention) was 83%. The 2 patients with irreversible TIPS occlusion had both received uncovered stents and died of variceal bleeding and hepatorenal syndrome at 2 days and 2 months after TIPS, respectively. All others remained free of symptoms. None underwent liver transplantation.In conclusion, ePTFE covered stents appear to result in increased TIPS patency and improved clinical outcome, as compared to uncovered stents and should therefore be recommended in all patients undergoing TIPS for BCS.

Preservation of the steatotic donor liver: machine perfusion versus cold storage

M. Bessems, B.M. Doorschodt, T.M. van Gulik. Surgical Laboratory, Dept of Surgery, Academic Medical Center, Amsterdam, The Netherlands

About 30-40% of all potential liver donors are not used because of advanced liver steatosis, a number which is increasing due to the increase of donors with obesitas and diabetes. These liver grafts burden the already scarce donor liver pool and lead to increased waiting lists. Steatotic livers are considered sub-optimal and have been shown to perform weakly after conventional cold storage, frequently resulting in primary graft non-function.
Hypothermic machine perfusion (MP) has been introduced for presservation of donor livers instead of cold storage (CS), and has been associated with superior preservation results. The aim of this study was to compare CS and MP for preservation of the steatotic donor liver.
Steatosis was induced in male Wistar rats by use of a choline-methionine-deficient diet. After 24 h CS using the University of Wisconsin solution (UW) or MP using the modified UW solution (UW-Gluconate), liver damage and liver function parameters were assessed in an isolated perfused rat liver model. During 60 min of normothermic oxygenated reperfusion with Krebs-Henseleit buffer, liver enzymes, perfusate flow, hyaluronic acid clearance, bile production, ammonia clearance, urea production, oxygen consumption and ATP levels were determined. Furthermore, liver biopsies were examined by HE-staining and transmission electron microscopy (TEM).
All animals developed 30-60% steatosis. Livers preserved by CS sustained significantly more damage as compared to MP (AST: 77 ± 12 versus 24 ± 2 IU/L, ALT: 178 ± 30 versus 13 ± 6 IU/L, LDH: 836 ± 66 versus 105 ± 24 IU/L). Bile production (151 ± 32 versus 264 ± 30 µL/h, respectively), ammonia clearance (2.4 ± 0.4 versus 4.1 ± 0.4 mMol/L/h), urea production (1.0 ± 0.1 versus 1.6 ± 0.1 mMol/L/h), oxygen consumption and ATP levels were all significantly better after MP in comparison with CS. These results were confirmed by histology and TEM.
In conclusion: Machine perfusion ameliorates preservation results of the steatotic rat liver as compared to cold storage. With this preservation technique, steatotic livers may be used for transplantation instead of discarded.

Efficacy of interferon-alpha for the treatment of lamivudine resistant chronic HBeAg-positive Hepatitis B virus infection.

W.F. Leemans[1], H.J. Flink[1], H.L.A. Janssen[1], H.G.M. Niesters[2], S.W. Schalm[1], R.A. de Man[1]. Depts of Gastroenterology & Hepatology[1] and Virology[2], Erasmus MC, University Medical Center Rotterdam, The Netherlands

Lamivudine is effective in controlling viral replication and liver inflammation, but has as major drawback the emergence of mutations in the viral DNA associated with resistance. The aim was to determine the effect of (peg-)interferon-α therapy after the emergence of lamivudine resistance. Seventeen HBeAg-positive patients were included in whom a mutation in the YMDD-motif emerged during lamivudine therapy. Nine patients received a prior course of interferon-α. Median treatment duration was 52 weeks (range 20-53). Six of seventeen patients received (peg-)interferon-lamivudine combination therapy. HBV genotypes were A (38%), D (38) and other/unknown (24%). Patients were evaluated at inclusion, week 16, 32, 52 and after 26 weeks of post-treatment follow-up. Fourteen of seventeen patients completed the study according to the protocol. At inclusion median ALT as times the upper limit of normal (xULN) was 3.30 (range 1.50-11.00), median viral load $9.38x10^9$ copies/mL (range $8.37x10^8$-$10.41x10^{10}$). Overall median change in ALT (xULN) in comparison to baseline was –1.50 at week 52 (p=0.047) and –1.85 at end of follow-up (p=0.064). Median change in HBV-DNA was –1.63 at week 52 (p=0.001) and –0.44 log10 copies/mL at end of follow-up (p=0.009).Two of seventeen patients responded (HBe-seroconversion, HBV-DNA <105 copies/mL at the end of follow-up). In contrast to non-responders these patients had faint signals in the Inno-LiPA assay. In conclusion our results in HBeAg-positive patients show a decrease in response to interferon therapy in the presence of a mutation in the YMDD-motif. Only if small amounts of mutant virus as determined by a weak signal in the LiPA assay are present, interferon therapy may be beneficial. Although speculative, there may be a role for early “add on” interferon therapy after the development of resistance. Future large-scale studies have to confirm our findings and investigate the underlying mechanism of decreased response.

Hepatic function assessed by 99mTc-mebrofenin scintigraphy correlates with liver histopathology in rat model of steatosis and steatohepatitis

R. Vetelainen[1], R. Bennink[2], C. De Bruin[2], AK van Vliet[1], TM van Gulik[1]. Depts of surgery[1] (Surgical laboratory) and Nuclear Medicine[2] Academic Medical Center, Amsterdam, The Netherlands

Currently the only accurate method to evaluate steatosis is a histological scoring of liver biopsy and no noninvasive methods are available to evaluate the progress and severity of steatosis. 99mTc-mebrofenin uptake is used to estimate preoperative liver function before hepatectomy. However, the utility of 99mTc-mebrofenin scintigraphy in steatosis and steatohepatitis in unclear. This study evaluates if 99mTc-mebrofenin scintigraphy could be used to correlate the hepatic function with structural changes related to steatosis and steatohepatitis in a rat model.Wistar rats (250-300g) were fed methione and choline deficient diet (MCDD) inducing hepatic steatosis and steatohepatitis 1,3,5 and 7 weeks (n=4 per time point). A group (n=4) served as baseline controls. 99mTc-mebrofenin pinhole scintigraphy was used to evaluate the hepatocyte 99mTc-mebrofenin uptake rate and the time of maximal hepatic uptake(T max). 99mTc-mebrofenin uptake rate was correlated with hepatocellular damage (ALT, AST, AST/ALT ratio), synthesis function (prothrombin time: PT-TT), inflammation (TNF-alpha in liver), liver triglycerides content and histopathology. MCD diet induced mild steatosis(<30% hepatocytes, no inflammatory activity) after one week and steatohepatitis after 5 weeks with the typical pathological features (>60% hepatocytes, increased inflammatory activity, mild fibrosis). T max was significantly slower in the steatotic rats ($p<0.05$).There was a strong, significant correlation between the severity of steatosis evaluated by histological score and 99mTc-mebrofenin uptake rate ($r=0.82$, $p<0.0001$). 99mTc-mebrofenin uptake rate also correlated independently with hepatic TNF-alpha ($r=0.52$, $p=0.0001$) and triglycerides contents ($r=0.82$, $p<0.0001$). The correlation with PT-TT was strong ($r= 0.071$, $p<0.001$) but weak with AST, ALT and AST/ALT ratio ($r=0.29$, $p< 0.02$, $r=0.32$, $p<0.02$ and $r=0.30$, $p<0.02$, respectively). 99mTc-mebrofenin scintigraphy correlates strongly with steatosis and steatohepatitis suggesting the utility 99m Tc-hepatobiliary scintigraphy as a noninvasive method for monitoring the disease progression in steatosis and steatohepatitis.

Polycystic liver disease is associated with PRKCSH and SEC63 mutations

E. Waanders[1], R.A. de Man[2], R.H.M. te Morsche[1], J.B.M.J. Jansen[1], J.P.H. Drenth[1]. Depts of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre[1] and Erasmus MC, University Medical Centre Rotterdam[2], The Netherlands

Autosomal dominant polycystic liver disease (PCLD) is a genetic heterogeneous disorder characterized by progressive development of multiple fluid-filled liver cysts. Recent positional cloning studies identified 2 separate genes, PRKCSH and SEC63, to be involved. These genes encode components of the molecular machinery involved in the processing of newly synthesized glycoproteins in the endoplasmic reticulum. It is unknown what the relative contribution of mutations in PRKCSH, SEC63 and other genes is in PCLD and whether PRKCSH and SEC63 gene mutations also cause mild, sporadic PCLD. The aim of this study was to identify mutations and assess their influence in PCLD.We selected patients with more than 2 liver cysts on radiological studies, and excluded those with renal cysts. A total of 43 patients with sporadic PCLD entered the study and 3 groups were distinguished: A, 2-10 cysts (12 patients); B, 11-20 cysts (10 patients) and C, more than 20 cysts (21 patients). We sequenced the complete open reading frame and in 11/43 (26%) we detected PRKCSH (n=4) or SEC63 (n=7) gene mutations. The PRKCSH mutations contained 2 missense and 2 splice site mutations and the SEC63 mutations included 3 missense and 1 deletion. There was no mutational hotspot in either gene and no relation between severity of disease and mutation prevalence. Two SEC63 mutation carriers were double heterozygous at the same locus for a second SEC63 mutation. There were no patients who had both PRKCSH and SEC63 mutations. In our series we observed a frequent PRKCSH variant (G871A) that changes the amino-acid composition (A291T) but the heterozygosity was comparable among patients (35%) and controls (38%). In conclusion PRKCSH and SEC63 mutations cause familial PCLD and sporadic PCLD. We observed a similar mutation frequency between patients with mild and severe disease. The data support the notion of considerable genetic heterogeneity and indicate that at least one more locus is associated with PCLD.

Evaluation of limited sampling strategy of ciclosporin-monitoring after liver transplantation using an individualized population pharmacokinetic model

P. Langers[1], S.C.L.M. Cremers[2], E.M.T. Rijnbeek[1], J. Ringers[3], C.H.B.W. Lamers[1], J. den Hartigh[2], B. van Hoek[1]. Dept of Gastroenterology & Hepatology[1] and Clinical Pharmacy & Toxicology[2] and Surgery[3], Leiden University Medical Center, The Netherlands

While C-0 monitoring of ciclosporin frequently results in overdosing and more renal dysfunction, C-2 monitoring may lead to episodes of underdosing and rejection and many subsequent adjustments. We devised a flexible individualized population pharmacokinetic model without the need for fixed sampling time points, which is accurate and easy to use in practice. After 18 months of using we evaluated our 0,1,2,3h-model concentrating on difference in dose, CRCL, dose adjustments and correlation with other models. From 30 patients we collected 152 0,1,2,3h-curves, and for several combinations of measured blood concentrations (0h; 1h; 2h; 3h; 0,1h; 0,2h; 0,3h; 1,2h; 1,3h; 2,3h; 0,1,2h; 0,1,3h; 0,2,3h; 1,2,3h) we calculated with the use of a computer program the area under the curve and the mean advised dose and looked at the correlation of these models with the 'gold standard' AUC0,1,2,3h and mean advised dose of our 0,1,2,3h-model. After switching from C-2 monitoring to our model there was no significant difference in daily ciclosporin dose (11±9 mg, p=0.237) or CRCL (5,2±4,1 ml/min, p=0.216). Two 2-point models and two 3-point models showed good correlation with our model (0,2h: r^2=0.88; 0,3h: r^2=0.87; 0,1,3h: r^2=0.91; 0,2,3h: r^2=0.92, all p<0.001) comparing their AUC's. Concerning the mean advised dose same models showed best correlation (r^2's respectively 0.88, 0.89, 0.94, 0.94, all p<0.001). Between and within patients there was large variability of blood levels with the same dose.
Conclusion: After switching from C-2 monitoring to our flexible limited sampling model without the need of fixed sampling time points on average there was no change in dose or kidney function. Some patients need less sampling points. This is feasible with our computer program which is easy to apply in practice.

Ex vivo gene therapy of the liver: new approach to tackle hepatitis C infection and recurrence after liver transplantation

S.D. Henry[1], P.G. van der Wegen[2], H.J. Metselaar[3], R. Bartenschlager[4], H.W. Tilanus[1], B.J. Scholte[2], L.J.W. van der Laan[1]. Depts of Surgery[1], Cell Biology[2] and Gastroenterology and Hepatology[3], Erasmus MC-University Medical Center, Rotterdam, The Netherlands and Dept of Molecular Virology[4], University of Heidelberg, Germany

Background: Chronic Hepatitis C Virus (HCV) infection is the leading indication for liver transplantation worldwide. However, re-infection of the graft by HCV causes progressive recurrence of liver disease and severely shortens the survival of patient and graft. Promising new approach to tackle this problem is to develop a retrovirus-based gene therapy for HCV that can be used during ex vivo perfusion of the liver graft prior to transplantation. Aim of the current study is to construct and test state-of-the-art lentiviral (LV) vectors that utilize RNA interference to prevent HCV infection.
Methods: The transduction efficiency of self-inactivated LV vectors was determined by green fluorescent protein (GFP) reporter gene expression. The anti-viral effect of the RNA interference therapy was tested in an HCV-replication model containing a luciferase reporter gene.
Results: Conditions for LV gene delivery to hepatocytes in the setting of graft perfusion and cold storage was investigated. Transduction of Huh-7 cells during 2 hour incubation with ice cold University of Wisconsin (UW) preservation solution was approx. 45%, which was similar to transduction in tissue culture medium at 37°C (40% GFP positive). Transduction was most effective with UW solution at 37°C (approx. 90%). Cells remained vital under all conditions. Several LV vectors expressing different small interfering RNA (siRNA) that target the HCV NS5 or 5′ untranslated regions were shown to be effective in inhibiting HCV replication in vitro.
Conclusion: This study has demonstrate that gene delivery by LV vectors can take place in UW preservation solution at 4°C, conditions similar to the cold ischemia of the graft. Furthermore, the gene therapy based on RNA interference was shown to be effective in reducing HCV replication. New vectors are being created that deliver multiple siRNA payloads which target different viral and host cell sequences simultaneously, thereby preventing mutational escape of HCV.

Interleukin-10 producing Lactococcus lactis for the treatment of Crohn's disease

H. Braat[1], P. Rottiers[2], N. Huyghebaert[3], E. Remaut[2], J-P. Remon[3], S. van Deventer[1], S. Neirynck[2,4], M.P. Peppelenbosch[5], L.S. Steidler[2,4] and D.W. Hommes[3]. Dept of Experimental Internal Medicine1, Academic Medical Center Amsterdam, The Netherlands, Dept for Molecular Biomedical Research[2] and Lab of of Pharmaceutical Technology [3], Ghent University, Belgium, Alimentary Pharmabiotic Centre[4], University College Cork, Cork, Ireland, Dept of Cell Biology[5], University of Groningen and Dept of Gastroenterology[6], Academic Medical Center Amsterdam, The Netherlands

Background: Systemic treatment of Crohn's disease patients with IL-10 lacks clinical efficacy but studies in animal models suggests that topical application of IL-10, using living genetically modified bacteria, can reduce disease activity. Treatment of patients with a living genetically modified bacterium poses questions to the safety of such a strategy for human subjects per se as well as to the biological containment of the transgene.
Methods: We treated 10 Crohn's disease patients for seven consecutive days with genetically modified *Lactococcus lactis* in which coding sequence for thymidylate synthase was replaced by IL-10 (LL-Thy12).
Results: Treatment with the bacterium was safe as only minor adverse events were being reported with flatulence being the most prominent temporary side effect. The feces collected on day 4 contained the largest amount of LL-Thy12-specific DNA sequences; 33.9% of total detected LL-Thy12-specific DNA sequences during the study period. Two days after termination of the therapy no such DNA sequences were detected anymore and no dissemination of the transgene to other microorganisms was observed. Finally, after one week of treatment patients showed a decrease in CDAI of an average of 71.7 ($P<0.02$, CI 95%).
Conclusions: Treatment with IL-10 producing Lactococcus lactis is clinically effective after one week of treatment without relevant side-effects, this novel therapy is especially suitable for maintenance therapy of Crohn's disease.

Five year's subjective and objective results of antireflux surgery: A randomized controlled trial of laparoscopic versus conventional Nissen fundoplication

W.A. Draaisma[1], H.G. Rijnhart-de Jong[1], I.A.M.J. Broeders[1], A.J.P.M. Smout[2], J. Oors[2], J. van der Scheur[2], E.J.B. Furnee[1], H.G. Gooszen[1,2]. Dept of Surgery[1] and Gastrointestinal Research Unit[2], University Medical Center Utrecht, The Netherlands

Several studies have shown the long-term success of antireflux surgery. Some of these show a gradual increase in recurrent gastro-esofageal reflux and also an increasing need for medical treatment. The purpose of this study was to investigate the subjective and objective results of laparoscopic (LNF) and conventional Nissen fundoplication (CNF) up to 5 years after surgery. From 1997 to 1999, 177 patients were randomized to undergo LNF or CNF. Five years after surgery a quantitative symptom score including a request for esophageal manometry and 24-hr pH metry was sent to all eligible patients. A total of 97 patients agreed with both objective and subjective follow-up; 48 patients in the LNF group and 49 in the CNF group. In both groups, 6 patients had undergone reoperation. These 12 patients were analysed separately (redo group). At 5 years follow-up, there was no difference in subjective outcome between LNF and CNF, 88% overall satisfaction respectively for both, redo patients scored lower with 79%. There was no difference in quality of life scores. Daily heartburn was reported in 4, 11 and 3 patients in the groups LNF, CNF and redo (n.s.), regurgitation in 4, 8 and 4 (n.s.). Mean total acid exposure percentage with pH < 4 were 2.3, 1.8 and 2.0 resp. For all 3 groups, there was no correlation between reflux symptoms and acid exposure (r=0.17; n.s., r=0.07; n.s. and r=0.5, n.s. resp). Medication (mainly antisecretory drugs), however, was taken in 11, 25 and 23% resp. (n.s.). We found no significant differences between objective and subjective results at three to six months and results obtained at five years after surgery. The effect of LNF and CNF on general state of health does not decrease with time and objective reflux control is sustained up to five years after surgery. The symptoms expressed at 5 years are not related to reflux and, consequently, the prescription of antisecretory drugs is often not based on objective evaluation of recurrent pathological reflux.

Arginine, citrulline, and nitric oxide metabolism in patients with Liver Failure and the effect of intervention with Hypothermia and transplantation

S.W. Olde Damink[1], S. Sen[2], R.P. Mookerjee[2], P.C. Hayes[3], N.E.P. Deutz[1], R. Jalan[2]. Dept of Surgery[1], Maastricht University, The Netherands, Institute of Hepatology[2], UCL, and Royal Infirmary[3], Edinburgh, United Kingdom

Background. The circulation in cirrhosis is characterised by progressive vasodilatation. Several studies suggest a critical role for increased nitric oxide (NO) synthesis as being central in the pathogenesis of the altered circulatory state but there are no quantitative data in humans. The aims of this study were to quantitatively determine the kinetics of arginine, citrulline and NO metabolism in patients with varying severities of liver disease and evaluate whether they are altered with interventions used to treat liver failure. Methods. 4 groups were studied; Patients: Well compensated cirrhosis (Gr 1. n=5, Pugh<7); Decompensated cirrhosis Gr 2. (n=7, Pugh>7), Acute-on-chronic liver failure (ACLF) (Gr 3. n=7, 1 or more organ failure) and Acute liver failure (ALF) (Gr 4. n=8, Fulfil poor prognosis criteria). Four patients with ALF were treated with hypothermia and 4 patients underwent liver transplantation (OLT). Arginine, Citrulline and NO metabolism were measured using a primed continuous infusion of a mixture of L-[15N2] Arginine and L-[13C;5,5-2H2] Citrulline. Plasma amino acid and tracer enrichments were measured using LC-MS. Results. The cardiac output was progressively greater in patients with more advanced liver disease (Gr 4>Gr 3>Gr 2> Gr1). Treatment of patients with hypothermia and transplantation resulted in a improvement in the circulatory state. Arginine levels and the kinetics of both arginine and citrulline were normal in liver failure. Whole body rate of appearance of NO was significantly greater in the liver failure groups (Gr 1: 33 (±8), Gr 2: 41 (±11), Gr 3: 64 (±13), Gr 4: 86 (±15) nmol NO/kg bw/min. Treatment of liverfailure significantly reduced NO appearance Gr 4+Hypo: 49 (±24) and Gr+OLT: 28 (±12) nmol/kg bw/min.
Conclusions: The data show absence of any significant derangements of arginine and citrulline production rates but a progressive increase in NO production with increasing severity of liver disease. Interventions that improve the haemodynamic state reduce NO production rates in these patients supporting the importance of NO in mediating the circulatory disturbance in liver failure.

Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis; A prospective randomised trial

D.L.Cahen[1], D.J. Gouma[2], Y. Nio[3], M. Delhaye[4], E.A.J. Rauws[1], M.A. Boermeester[2], O.R. Busch[2], J. Stoker[3], J.S. Laméris[3], M.G.W. Dijkgraaf[5], K. Huibregtse[1], J. Devière[4], M.J. Bruno1. Dept of Gastroenterology and Hepatology[1], Surgery[2] and Radiology[3], Academic Medical Centre, Amsterdam, The Netherlands. Dept of Gastroenterology and Hepatology[4], Hôpital Erasme, Brussels, Belgium. Dept of Clinical Epidemiology and Biostatistics[5], Academic Medical Centre Amsterdam, The Netherlands

Objectives: Increased pancreatic pressure due to ductal obstruction is considered one of the mechanisms of pain in chronic pancreatitis (CP). In symptomatic patients with a dilated pancreatic duct (PD), ductal decompression is therefore advocated. This prospective randomised trial compares endoscopic and surgical drainage of the PD.Methods: All symptomatic CP patients with a dominant PD obstruction (due to strictures and/or stones), without an inflammatory mass, were eligible for this study. Patients were randomised between endoscopic drainage by stent insertion (preceded by extracorporeal shock wave lithotripsy (ESWL) in Brussels if indicated) and surgical drainage by pancreaticojejunostomy (PJS). Primary endpoint was the average Izbicki pain score, measured during the 2 years of follow-up. Secondary endpoints were clinical success (> 50% decrease in pain score), morbidity, mortality and intervention rate. Results: In Oct. 2004 the study was discontinued after an interim analysis revealed a highly significant difference in primary endpoints. From 2000, 39 patients were included; 19 were treated endoscopically (16 underwent ESWL, median stent duration 27 weeks) and 20 were operated upon.During a median follow up of 24 months (range 6-24), the average pain score was significantly less after surgical drainage (51 versus 25, p=0.001). Moreover, pain response after surgery was immediate (<6 weeks) and consistent during follow-up. Furthermore, clinical success rates were 32 and 75% for endoscopic and surgical drainage respectively. One patient taking high dose NSAID's died 4 days after ESWL from a perforated duodenal ulcer. Complication rates were similar for both groups but endoscopic treatment required more therapeutic interventions (5 versus 1, p<0.001).
Conclusions: In this series of patients with advanced CP, surgical drainage of the PD was more effective than endoscopic treatment. Moreover, surgery resulted in more rapid pain relief and required less interventions.

Restorative Proctocolectomy in 2005
Prof. R.J. Nicholls

Modern surgical treatment for ulcerative colitis started in the late 1940s with the introduction of colectomy with ileostomy by Miller and colleagues. Excision of the disease led to a fall of mortality from over 30% after colonic diversion procedures to less than 5%. The resulting ileostomy proved technically difficult for patients to manage and this was largely resolved by the introduction of the everted ileostomy by Brooke in the early 1950s. By 1960 proctocolectomy was the accepted surgical treatment for ulcerative colitis. Mortality was low, colonic cancer risk was abolished and there was high patient satisfaction.
Attempts to avoid a permanent ileostomy were made in parallel. Colectomy with ileorectal anastomosis was developed from the 1940s onward, and still has a place in modern practice although it is now infrequently performed. Restorative proctocolectomy (RPC) was developped from the 1940s with the introduction by Ravitch and Sabiston of proctocolectomy with straight ileoanal anastomosis. The functional results were reviewed by Bacon in the 1950s and found to be variable. He proposed the interposition of a reservoir to reduce frequency and urgency of defaecation which often followed the straight ileo-anal operation. This technique was not applied to man at the time. Kock in the 1960s developed the continent ileostomy and continent urostomy, demonstrating that an ileal reservoir was compatible with health in patients. These various developments were combined by Parks in the 1970s. The colon and rectum were removed, the anal sphincter preserved, an ileal reservoir constructed and an ileoanal anastomosis performed. The operation, restorative proctocolectomy with ileal reservoir, has become the most commonly used procedure for ulcerative colitis when surgery is required. It has also been applied to many patients with familial adenomatous polyposis (FAP).

All departments working in the field have seen a steady fall in the numbers of conventional proctocolectomy with an increase in RPC and a substantial reduction in colectomy with ileorectal anastomosis. There has been argument over the indications in ulcerative colitis but failure in patients with Crohn's disease is high and those with sclerosing cholangitis have a high incidence of pouchitis subsequently. Severely ill patients should have an initial colectomy to be followed by RPC after an interval of four or more months. RPC is suitable where there is an established cancer provided accepted criteria for restorative surgery are observed. Females of child bearing age have a significant reduction in fertility to less than 50% of the normal population, those with colitis not undergoing surgery or patients having a colectomy. A strategy for such patients might involve an

initial colectomy allowing recovery of normal health and establishing a family before undertaking RPC.

There is now an experience of 28 years of the operation. Complications occur in 20-60% of cases and failure ranges from less than 5% to over 15%. Failure is related to the duration of follow up. It increases steadily from about 5% at 5 years to over 10% at 15-20 years. Sepsis, poor function and pouchitis are responsible for failure in about 50%, 30% and 10% of cases respectively. Patients who have pelvic sepsis in the early post operative period have a subsequent failure rate about five times that of the global population. Aspects of technique, including the mode of ileoanal anastomosis will be discussed. Long term outcome of patients with ulcerative colitis and FAP will be given.

Where failure is threatened by complications, salvage surgery may be applicable. Where this takes the form of abdominal surgery, the possible benefit must be set against the morbidity of excision of the pouch. This is significant, particularly relating to the perineal wound, re-admissions and the possibility of short bowel syndrome. Abdominal salvage procedures for **pelvic sepsis** have a wide range of success from 20% to over 80%. The reason for this difference is unclear but the duration and accuracy of follow up is undoubtedly a factor. There is a failure rate subsequent to salvage abdominal surgery which over a five year period is of the order of 30%. **Pouch-vaginal fistula** occurs in 5-10% of females. If high, abdominal advancement has an 80% chance of success, if low a perineal approach is effective in 60-65% of patients. Patients with pouch-vaginal fistula due to Crohn's disease uniformly fail. **Poor function** should be investigated in a formal manner. Where this is due to outlet obstruction at the ileo-anal anastomosis level, salvage surgery is effective in 60-80% of patients. Stenosis or a retained rectum are fairly common causes of out-flow obstruction. Where salvage surgery is successful in these groups, frequency of defaecation, urgency and incontinence are all improved. Pre-operative and post operative risk factors for a successful or poor out-come have been defined and should be useful to patients as an indication of prognosis.

Villous atrophy occurs in the ileal pouch mucosa whether the patient had ulcerative colitis or FAP. Acute inflammation leading to the clinical con-dition of **pouchitis** occurs in colitic patients; there is controversy as to whether this occurs in FAP. Cumulative rates of pouchitis over a 5-10 year period amount to around 50%. In many of these patients only one or two episodes occur during the period of follow up but in about 5% of the total patient group, chronic unremitting inflammation of the pouch is present. There is an increase in faecal bacterial counts within the reservoir

of about 10 million times compared with the terminal ileum following construction. It is highly likely that this contributes to pouchitis in susceptible individuals. Antibiotic treatment is usually effective, but relapse often occurs. Maintenance therapy after an induced remission by antibiotics using oral probiotic bacteria has been shown significantly to reduce the chance of remission.
Recently there has been interest in the long term development of dysplasia and occasionally in a few patients. The sites at risk include the ileal mucosa itself and the residual large bowel columnar epithelium below the ileo-anal anastomosis. The risk of dysplasia in the ileal pouch is very low over a follow-up period of 15 or more years. A few cancers distal to the anastomosis have now been described where dysplasia or carcinoma in the original surgical specimen appears to be a risk factor.

Restorative proctocolectomy should be carried out in units with a general competence to manage inflammatory bowel disease and FAP. The unit should contain surgeons.gastroenterologists, and histopathologists, as well as specialist nurses, dietician, stoma therapist and psychologist. In this way multi-disciplinary care will be offer the patient best care including appropriate decision taking and adequate long term management.

High-Resolution Endoscopy Is More Important Than Chromo-endoscopy or Narrow Band Imaging For Detecting High grade Intraepithelial Neoplasia (HGIN) in Barrett Esophagus: A Prospective Randomized Cross-Over Study

M.A. Kara[1], F.P. Peters[1], W.D. Rosmolen[1], K.K. Krishnadath[1], F.J.W. ten Kate[2], A.C. Bultje[3], P. Fockens[1], J.J.G.H.M. Bergman[1]. Depts of Gastroenterology and Hepatlogy[1], Pathology[2] and Biostatistics and Epidemiology[3], Academic Medical Center Amsterdam, The Netherlands

Background: High resolution endoscopy (HRE) in combination with indigo carmine chromoendoscopy (ICC) or narrow band imaging (NBI) may improve the detection of HGIN in Barrett esophagus (BE). We conducted a randomized cross-over study to compare HRE-ICC with HRE-NBI for detecting HGIN in BE.Patients and Methods: We included BE patients who were referred for work-up of endoscopically inconspicuous HGIN (n=17), scheduled for follow-up after endoscopic treatment for HGIN (n=6), or scheduled for regular surveillance (n=5). All 28 patients underwent two procedures, HRE-ICC and HRE-NBI (6 weeks interval), in a randomized sequence. The two procedures were performed by two experienced endoscopists who were blinded to the findings of the other examination. A high-resolution zoom endoscope (Q240Z, Olympus) and a prototype NBI-system (Olympus, Tokyo, Japan) were used in all examinations. The BE was first inspected with HRE without using the zoom mode followed by detailed inspection (overview and zoom) with ICC or NBI. Two targeted biopsies were taken from detected lesions followed by 2-cm-interval-4-quadrant biopsies. Pathologists were blinded to the imaging technique used. Results: Using the combined histology results of the two procedures, 14 patients were diagnosed with HGIN. Both techniques identified 11 patients (79%) with HGIN by targeted biopsies and in all these patients HRE was sufficient to detect at least one lesion with HGIN. ICC and NBI detected additional lesions with HGIN occult to HRE in 2 and 3 patients, respectively, without increasing the number of patients diagnosed with HGIN.
Conclusion: In this group of high-risk BE patients, HRE performed by experienced endoscopists led to the identification of most patients with HGIN. In this setting, ICC and NBI are more suited for targeted detailed inspection and delineation of lesions than for primary detection of HGIN. HRE should be considered the imaging technique of choice in patients with BE.

Double balloon enteroscopy: The Dutch one year Experience. Indications, Yield, and Complications in a series of 125 cases

G.D.N. Heine[1], M. Hadithi[1], M.J.M. Groenen[2], E.J. Kuipers[2], M.A.J.M. Jacobs[1], C.J.J. Mulder[1]. Dept of Gastroenterology[1], VU University Medical Center, Amsterdam, Dept of Gastroenterology and Hepatology[2], Erasmus MC, University Medical Center Rotterdam, The Netherlands

With the advent of the double balloon endoscopy method (DBE, Fujinon Japan) enabling true full length enteroscopy for the first time, a major shortcoming of conventional methods has been surpassed. With this new technique 125 patients were investigated in the first year after introduction in the Netherlands in September 2003. The results of this series with regard to indications, diagnostic yield, therapeutic interventions and safety are presented. Double balloon enteroscopy was performed in 125 patients. The main indication was unidentified GI blood loss (80/125 =64%), followed by refractory celiac disease(17/125 =13,6%), suspected Crohn's disease (9/125 =7,2%), hereditary tumours (8/125 =6,4%), others(8/125 =6,4%), and protein losing enteropathy(3/125 =2,4%). Insertion length was measured. Treatment of angiodysplasias was performed upon antegrade encounter. All patients were monitored for complications. 122 patients were approached orally, 3 via the colon, 11 from both sides. Average insertion length was 280 cm. The average procedure duration was 82 min (range 55 to 190). An explanation for GI blood loss was found in (56/80=70%) mostly angiodysplasias of which almost 100 % were removed without further blood loss after 2,2 consecutive DBE + APC sessions. Surprisingly also 6 malignant neoplasias (4 lymphoma's/ 2 melanoma's) were found in the GI blood loss group. In the refractory celiacs (4/17=23,5%) EATLs were diagnosed. Crohn's disease was diagnosed in (2/9= 22,2 %). Protein losing enteropathy revealed a lymphoma in one and lymphangiectasia in another case. Patient tolerability was excellent. Two complications occurred: one perforation in treatment for Peutz Jeghers obstruction, one case of mild pancreatitis.
Conclusion: Double balloon enteroscopy is a safe endoscopic technique with a high diagnostic yield in selected patients and excellent patient tolerability. In the group with GI blood loss a surprising number of malignant neoplasias are found.

The prevalence of K-ras mutations in ductal brush cytology and bile of subjects without pancreatic disease using the epidemiologic necropsy as study design

N.T. van Heek[1], E. Caspers[2], M. Tascilar[2], A. Musler[2], M. Polak[2], D.J. Gouma[1], P. Drillenburg[2], G.J.A. Offerhaus[2]. Depts of Surgery[1] and Pathology[2], Academic Medical Center Amsterdam, The Netherlands

IntroductionPancreatic cancer has a poor prognosis. Surgical resection and surveillance of subjects at risk for pancreatic cancer are only useful in an early stage of the disease. Although the K-ras oncogene is mutated in >90% of pancreatic cancers, its specificity as a screening marker remains a concern. The aim of this study was to estimate the prevalence of K-ras mutations in brush cytology and bile in the non-diseased general population by using the ”epidemiologic necropsy” study design. Methods During one year all necropsies were prospectively included and categorized by age group, gender and cause of death. After brushing the distal common bile duct for cytology and squeezing the gallbladder for bile, the underlying pancreatic tissue was resected. DNA was isolated and subjected to PCR amplification for K-ras codon 12 mutations. Randomly selected pancreatic tissue was analyzed for the presence of pancreatic intraepithelial neoplasia (PanIN) lesions. The prevalence of K-ras mutations in brush and bile from necropsies was translated towards the general population by direct standardization using the demographics of the Dutch population. Results After exclusion of 14 necropsies for related disease, 317 necropsies consisting of 187 men and 130 women were available for analysis. K-ras mutations were detected in 78/317 (25%) brush cytology specimens and 18/317 (6%) bile specimens. The prevalence of K-ras mutations in the general population could be estimated at 14% in brush cytology and 3% in bile. K-ras mutations were only detected in pancreatic tissue carrying PanIN-1A and PanIN-1B lesions, which were present in 95%.
Conclusions: Given the prevalence of K-ras mutations in brush cytology and bile in the non-diseased population and the high rate of mutations in the commonly detectable PanIN-1A and PanIN-1B, the concerns regarding specificity of K-ras mutation analysis seems justified. Certainly as a screening test in the population not at risk this method cannot be used.

Attendance at surveillance endoscopy in patients with adenoma or colorectal cancer

S.A. Mulder[1], M.E. van Leerdam[2], R.J.Th. Ouwendijk[1], R.W.M. Giard[3], D.J. Bac[1], E.J. Kuipers[2]. Dept of Internal Medicine[1], Ikazia Hospital, Dept of Gastroenterology and Hepatology[2], Erasmus MC, Dept of Pathology[3], Medical Centre Rijnmond Zuid and Ikazia Hospital, Rotterdam, The Netherlands

Introduction: Surveillance in patients treated for adenoma or colorectal cancer (CRC) reduces mortality from CRC. In most Dutch clinical practices, removal of adenoma or CRC is followed by an advice for follow-up endoscopy, but does not include active invitation. To which extent this passive policy affects the efficacy of surveillance is unknown, but is of major importance in view of the current increasing interest to move ahead with screening and surveillance for colorectal neoplasia.
Aim: To assess the yield of surveillance without active invitation for follow-up endoscopy. Methods: Cohort follow-up of patients ≤75 years diagnosed between 1997-1999 with polyps or CRC at index endoscopy. The interval of follow-up endoscopy was determined until October 2004. Patients with familial adenomatous polyposis, hereditary nonpolyposis CRC, inflamematory bowel disease were excluded.
Results: 3078 patients ≤75 years underwent colonoscopy in the period 1997-1999. 391 patients (13%, M/F 228/163, mean age 60 yrs) were newly diagnosed with a polyp (n=268) or CRC (n=123). Adenomatous polyps were present in 155/268 (58%) patients, no histology was available in 30%. Among patients with adenomatous polyps, only 67/155 (43%) had surveillance endoscopy within the recommended 1 year (according to the at that time available guideline) and 59/155 (38%) did not have any follow-up at all.
CRC was diagnosed in 123 patients, 44% of them had follow-up within 1 year after surgery, 36% did not have any surveillance at all. During follow-up CRC was found in 7 patients including 4 with polyps and 3 with CRC at index endoscopy.
Conclusions: In surveillance for colorectal neoplasia active follow-up invitation appears of paramount importance. Passive follow-up policies lead to major underperformance of surveillance programs. This means that individual centers should for now start and maintain local databases while awaiting further regional and nationwide surveillance programs for colorectal neoplasia.

Correlation of a simple endoscopic scoring system of rectal wall toxicity with dose surface maps after prostate irradiation

D.J. de Jong[1], L.P. van der Vight[2], E.N.J.Th van Lin[2], A.L Hoffmann[2], M.E.P. Philippens[2], A.G. Visser[2]. Depts of Gastroenterology & Hepatology[1] and Radiation Oncology[2], Radboud University Nijmegen Medical Centre, The Netherlands

Radiation induced rectal toxicity is a limiting factor for prostate cancer, which is related to the radiation dose and the volume of the rectum involved. The purpose is to compare rectal toxicity, assessed by endoscopy, with rectal wall dose surface maps after prostate radiotherapy, with and without an endorectal balloon (ERB). Forty-eight patients received 4-field conformal radiotherapy (67,5 Gy). Twenty-three patients were included in the ERB group and 25 in the non-ERB group. Rectal toxicity was scored by sigmoidoscopy after 3,6 and 12 months. The rectum was evaluated for telangiectasia, congestion, ulceration, strictures and necrosis. All items were scored for the anterior, posterior and lateral wall for 4 distances from the anus, resulting in 12 mucosal areas. Primary endpoint was presence of different grades of telangiectasia after 1 year. With virtual rectum unfolding, angular rectal wall radiation dose surface maps were generated. For dose-response analysis, dose of each mucosal area was reduced to a single dose value using the equivalent uniform dose (EUD). The dose-response data were used to estimate the EUD at fifty percent probability of telangiectasia (EUD50-T) by a probit analysis. One year after radiotherapy, no ulceration, strictures or necrosis have been observed. Congestion was only apparent at 3-month. A clear correlation between radiation dose and development of telangiectasia was observed. After 1 year, in the non-ERB group and ERB group, telangiectasia were observed in 25.4 % and 16.2 % ($p< 0.001$) of all areas. The high dose (>60 Gy) volume for the non-ERB group was 23.5% of all mucosal areas, and 16.4 % ($p<0.05$) for the ERB group. The EUD50-T was 41 Gy and 58 Gy, respectively, for non-ERB group and ERB group. In conclusion, a strong correlation between endoscopic grading of telangiectasia and dose surface mapping was observed. Use of the ERB reduced the total high-dose volume of the rectal wall and reduced rectal toxicity.

The role of video capsule edoscopy in the diagnosis and management of Crohns disease

K.F. Bruin[1], K.M.A.J. Tytgat[2], E.M. Mathus-Vliegen[1], D.W. Hommes[1], P. Fockens[1]. Dept of Gastroenterology[1], Academic Medical Center, Amsterdam and Dept of Gastroenterology[2], Medical Center Alkmaar, The Netherlands

Crohn's disease (CD) of the small bowel still presents many diagnostic difficulties. Two patient categories can be especially difficult to manage. The first group consists of patients with abdominal complaints without a prior history of CD and negative ileocolonoscopy and enteroclysis, but with either raised inflammatory parameters upon laboratory investigation, diarrhea or weight loss (group I). The second group consists of patients already known with CD, who present with complaints suggestive of an exacerbation, but with negative ileocolonoscopy and enteroclysis (group II). Video capsule endoscopy (VCE) could be helpful in determining patient management in these groups. In this abstract, we describe our experience with VCE in these groups. VCE was performed using the Given M2A system, according to standard protocol in our institution. Between September 2001 and September 2004, 31 VCEs were performed in patients with known or suspected CD. Three patients were studied twice because of recurring or persisting symptoms. The coecum was visualized in 70% of the procedures. Group I consisted of 9 patients. In 3 of these, CD was confirmed by VCE, in 5 patients CD became unlikely and in one findings were equivocal. Group II consisted of 19 patients. Twelve showed active disease, in 6 patients no disease activity was seen, and in one findings were equivocal. Thus, in these 31 examinations, a diagnosis of either active or inactive CD could be made in 73% (52% active CD) and in 15% CD could be ruled out as a cause of the patient's complaints. In 52% a change in patient management followed VCE and in 48% a wait and see policy was followed after VCE. VCE is a valuable tool in the evaluation of these patient groups. The finding of active disease always led to a change in patient management. Excluding CD activity in the small bowel prevented unnecessary treatment and further investigations.

Evidence illustrating the need for dysplasia screening in patients with longstanding achalasia

G.E. Boeckxstaens[1], C.B. Verkleij[1], J.J. Bergman[1], J.F. Bartelsman[1], J. Offerhaus[2], G.N. Tytgat[1]. Depts of Gastroenterology[1] and pathology [2], Academic Medical Center Amsterdam, The Netherlands

In a previous study, we confirmed that esophageal carcinoma is a major cause of death in patients with longstanding achalasia. At present, the need for screening remains however controversial especially as data on the prevalence and especially the progression of dysplasia is lacking. Therefore, a prospective study was designed to screen for dysplasia in patients with longstanding achalasia. Thirty six patients (32 - 86 yr, 22 M) with longstanding achalasia (5-10 yrs: n=4, 10-15 yrs: n=11, >15 yrs: n=21) were invited to undergo an upper endoscopy. Biopsies were taken in each quadrant every 3 cm over the entire length of the esophagus and from suspicious lesions identified during conventional endoscopy or after Lugol staining. Subsequently, patients were included in an endoscopic screening program (repeat upper endoscopy with Lugol staining). At the first endoscopy, 2 out of 36 (5.5 %) patients had low grade dysplasia, detected by Lugol staining only. In the subsequent 3 yr follow (yearly endoscopy), this lesion remained stable in one of the two patients. The other has only been diagnosed recently. Three years later, 18 patients with a negative initial study agreed to undergo a second endoscopy. Of these patients, one patient had a malignant ulcer at 38 cm from the incisors, staged as a type IIb to III lesion. Another patient had an abnormal staining pattern during Lugol staining starting at the top margin of the gastric folds extending to 25 cm from the incisors. Biopsies of this IIa-IIb lesion revealed carcinoma in situ, compatible with a superficially spreading squamous carcinoma (TisM0N0).
Conclusions: Our study shows that patients with longstanding achalasia have a high risk (11 %) to develop esophageal dysplasia or malignancy. Based on these findings, we conclude that screening endoscopy with Lugol staining should be performed in patients with longstanding achalasia, preferentially at a time interval of three years or even shorter.

Use of acid suppressive drugs by patients with Barrett's esophagus reduces the risk of esophageal adenocarcinoma

P.J.F. de Jonge[1], L.M.M. Wolters[1], E.J. Kuipers[1], P. Honkoop[1], E.W. Steyerberg[2], P.D. Siersema[1]. Depts of Gastroenterology & Hepatology[1] and Public Health[2], Erasmus MC University Medical Center Rotterdam, The Netherlands

Factors leading to an increased risk of development of esophageal adenocarcinoma (EAC) in patients with Barrett's esophagus (BE) are poorly understood. We conducted an epidemiologic investigation of possible associations between BE and EAC. We performed a hospital-based case-control study in the south-west of The Netherlands. Cases were patients with EAC and controls were subjects with long-segment BE (intestinal metaplasia; >2 cm). Information on the subjects' history of diet habits, physical activity, gastroesophageal reflux disease (GERD), use of proton-pump inhibitors (PPIs) and H2-receptor antagonists (H2RAs), and family history of GERD, BE and esophageal and gastric cancer was collected by questionnaires. Odds ratios (OR) were calculated by logistic regression, with multivariate adjustment for the potentially confounding variables sex, age and educational level.A total of 67 cases (90% men; mean age: 62 ± 10 yr) and 71 controls (61% men; mean age: 57 ± 12 yr) were included. Cases with EAC had more frequently been working in a forward bending position (OR: 3.8 (95%CI: 1.4–10.4) but had less frequently recurrent symptoms of heartburn or regurgitation (OR: 0.3 (95%CI: 0.1–0.6) and 0.3 (95%CI: 0.1–0.6), resp.). The longer-lasting the symptoms of reflux, the stronger the protective effect of developing EAC (OR heartburn: 0.3 (95%CI: 0.1-0.8), OR regurgitation: 0.3 (95%CI: 0.1–0.8)). Controls with BE had more frequently been using PPIs or H2RAs (OR: 0.1 (95%CI: 0.02–0.2) and 0.3 (95%CI: 0.1–0.8), resp.) This protective effect increased if acid suppressive drugs had been taken for a period of at least two years, compared to sporadic use (OR PPIs: 0.03 (95%CI: 0.01–0.10) and H2RAs: 0.34 (95%CI: 0.12–0.96)).
Conclusion: Longstanding symptoms of GERD and a prolonged use of acid suppressive drugs are associated with a reduced risk for the development of EAC in BE.

Length of Barrett's esophagus is determined by size of a hiatus hernia and use of proton-pump inhibitors

M. Kerkhof[1], E.W. Steyerberg[2], J.G. Kusters[1], E.J. Kuipers[1], P.D. Siersema[1], for the CYBAR-study group. Depts of Gastroenterology and Hepatology[1] and Public Health[2], Erasmus MC, Rotterdam, The Netherlands

It is known that the length of a Barrett's esophagus (BE), a premalignant disorder of the esophagus, is associated with an increased risk of neoplastic progression. It is however not known which factors determine the length of BE, but gastro-esophageal reflux disease (GERD) is likely to play a role.
The aim of this study was to determine the relationship between the length of BE, and the size of a hiatus hernia (HH), use of proton-pump inhibitors (PPIs), GERD symptoms and reflux esophagitis (RE).
Between October 2003 and December 2004, 805 patients with BE were included in the CYBAR-study. BE was diagnosed endoscopically (≥ 2 cm) and histologically (intestinal metaplasia). The length of the Barrett's segment, the size of the HH and the presence of RE (Los Angeles classification) were documented. In addition, symptoms of GERD and duration of PPI use were registered.
Mean length of BE was 4.4 ± 2.6 cm, whereas mean size of HH was 3.0 ± 2.0 cm. In total, 725/805 (90%) patients used PPIs and had used them for a mean period of 41 ± 37 months. At entry, 81/805 (10%) patients had RE, with grade A in 29 patients, grade B in 38, grade C in 7 and grade D in 3 patients (3 unknown). GERD symptoms were present in 241/805 (30%) patients, mainly heartburn and regurgitation. A positive correlation was found between the size of the HH and BE length (Pearson's correlation coefficient: 0.27; $p<0.001$). For each 1 cm increase in size of HH, BE length increased by 0.34 cm. BE length correlated inversely with PPI use ($p<0.05$), but not with duration of use. BE length did not correlate with GERD symptoms, nor with severity of RE.
Conclusion: The correlation with HH size, and inverse relationship with PPI use, suggests a role for GERD in establishing the length of the BE segment. The early introduction of anti-reflux measures may minimize or even prevent the development of BE and in that way prevent esophageal adenocarcinoma.

Ultrasound or CT scan for the detection of supraclavicular lymph nodes in patients with esophageal carcinoma

E.P.M. van Vliet[1], A. van der Lugt[2], E.J. Kuipers[1], H.W. Tilanus[3], A. van der Gaast[4], P.D. Siersema[1]. Depts of Gastroenterology[1], Radiology[2], Surgery[3] and Oncology[4], Erasmus MC/University Medical Center Rotterdam, The Netherlands

Malignant supraclavicular lymph nodes in patients with thoracic esophageal carcinoma are considered to be distant metastases. Both ultrasound (US) and CT scan (CT) are used to detect these metastases. It is not known whether either one or both investigations should be used to investigate the supraclavicular region. In this study, we compared US, if indicated with fine-needle aspiration (FNA), and CT for the detection of supraclavicular lymph node metastases in esophageal cancer patients.
From 1994 to 2004, 567 patients with esophageal carcinoma underwent US and CT, both including the supraclavicular region, for staging of esophageal cancer. In only 108 CT reports, the radiologist explicitly mentioned the presence or absence of abnormalities in the supraclavicular region and these patients were included in this analysis. The gold standard was a radiological result with ≥6 months of clinical follow-up (N=69), cytological confirmation of malignancy (N=33) or post-operative detection of malignant lymph nodes in the supraclavicular region in the resected specimen (N=6).
Sensitivity of US with FNA for malignant supraclavicular lymph nodes was 74% (20/27), whereas this was 59% (16/27) for CT. Specificity was 100% (81/81) and 98% (79/81), respectively. Before performing FNA, US had classified 21 lymph node(s) as being malignant, resulting in a sensitivity of 78% (21/27) and specificity of 88% (71/81). In 3 patients with a positive gold standard (FNA (2), radiological result with ≥6 months of follow-up (1)), only CT classified supraclavicular lymph nodes as being malignant, whereas the initial US was negative. In 2 of these patients, a second US was positive and in 1 patient, the US was not repeated.
Conclusion: Both US with FNA and CT of the supraclavicular region should probably be used in patients with thoracic esophageal carcinoma to detect metastases, however a blinded, comparative study is needed to confirm these results.

Neoadjuvant selective COX-2 inhibition downregulates important oncogenic pathways in patients with esophageal adenocarcinoma

J.B. Tuynman[1,2], C.J. Buskens[1], K. Kemper[2], F.J.W. ten Kate[3], G.J.A. Offerhaus[3], D.J. Richel [2], J.J.B. van Lanschot[1]. Depts of surgery[1], Medical Oncology [2] and Pathology[3], Academic Medical Center, Amsterdam, The Netherlands

Regular use of NSAIDs and selective cyclooxygenase-2 (COX-2) inhibitors is associated with a risk reduction in the development of esophageal adenocarcinoma. In vitro data show that selective COX-2 inhibitors induce apoptosis and down regulate oncogenic pathways. However, the significance of these findings in vivo is unknown. Therefore, the aim of this study was to evaluate the effects of neoadjuvant therapy with the selective COX-2 inhibitor celecoxib in patients with esophageal adenocarcinoma on molecular mechanisms involved in carcinogenesis and dissemination.12 patients with esophageal adeno carcinoma were included for neoadjuvant treatment (4 weeks) with celecoxib at 400mg twice a day. Biological changes were evaluated using a prospectively included patient control group, not receiving NSAIDs or celecoxib and evaluated before and after treatment. A tissue microarray was made to evaluate protein expression levels by immunohistochemistry. RNA levels of COX-2 and c-MET were determined quantitatively with RT-PCR. Esophageal adenocancer cell lines were used to asses the in vitro effects. Celecoxib administration resulted in decreased cell viability, increased apoptosis and decreased COX-2 and c-MET expression in vitro. In patients, we observed a significant down regulation of COX-2 (40% reduction, p=0.002) and c-MET (30% reduction, p=0.005) after treatment compared to the control group. In agreement, a significant down regulation of tumoral COX-2 (P=0.002) and c-MET (P=0.0002) expression was observed before and after treatment. No side effects or postoperative morbidity associated with celecoxib was observed. This is the first study to demonstrate both in vitro and in vivo that selective COX-2 inhibition down regulates COX-2 and c-MET expression in esophageal adenocarcinoma.
We conclude that neo-adjuvant therapy with celecoxib attenuates important oncogenic pathways and might have clinical potential in patients with esophageal adenocarcinoma.

Barrett's esophagus is associated with a predominant humoral immune response

L.M.G. Moons[1], J.G. Kusters[1], E. Bultman[1], E.J. Kuipers[1], W.H.M. Tra[1], J. Kwekkeboom[1], H. van Dekken[2], A.H.M. van Vliet[1], P.D. Siersema[1]. Dept of Gastroenterology & Hepatology[1] and Pathology[2], Erasmus MC, Rotterdam, The Netherlands

Barrett's esophagus (BE) is associated with a chronic inflammatory response marked by a local increase of IL-4 and IL-10 transcription. To determine whether BE is indeed associated with a switch towards a Th2 type response, the numbers of Th2 effector cells (plasma cells and mast cells) and Th1 effector cells (macrophages and cytotoxic T cells) were quantified in 174 esophageal biopsies [112 from 20 BE and 62 from 20 reflux esophagitis (RE) patients] by immunohistochemistry. In addition, the antibody classes produced by plasma cells (IgA, IgG, IgM or IgE), and the presence of isolated lymph follicles (segregated B- and T cell areas, follicular dendritic cells (CD23), and expression of CXCL13) were analyzed by immunohistochemistry. In RE, 115±23 (mean ± SEM) inflammatory cells per microscopic field (400x) were observed consisting of plasma cells (22±10; 19%), mast cells (17±4; 15%), macrophages (47±10; 41%), and cytotoxic T cells (29±8; 25%). In BE, the total number of inflammatory cells was 230±16. This increase in inflammatory cells was mainly due to a higher number of plasma cells (93±12; 40%; $p<0.001$) and mast cells (41±4; 18%; $p<0.001$). The relative proportion of macrophages (63±3; 27%; $p<0.05$) but not cytotoxic T cells (33±3; 15%) was decreased in BE compared to RE. More than 90% of the plasma cells in RE and BE expressed IgG, with the remaining cells expressing IgA, IgE, and IgM. A stain for IgE and plasma cells showed IgE+ plasma cells in BE. Isolated lymph follicles (ILFs) were present in 6/20 patients with BE, but not RE ($p<0.001$).
Conclusions: When compared to RE, the inflammatory response in BE was characterized by an increase in Th2 effector cells and formation of ILFs. These findings indicate that BE is characterized by a predominant humoral immune response. Since inflammatory conditions that are associated with a predominant humoral immunity often predispose to cancer, the observed shift may contribute to the risk of neoplastic progression in BE.

The prognostic distinction between Barrett's oesophagus with and without specialised intestinal metaplasia is irrational

M. van Blankenstein[1], C.W.N. Looman[2]. Depts of Gastroenterology & Hepatology[1] and Public Health[2], Erasmus MC, Rotterdam, The Netherlands

For presumably pragmatic reasons, the definition of Barrett's oesophagus (BO) has been narrowed down to columnar lined oesophagus (CLO) containing specialised intestinal metaplasia (SIM), as only this form was found to be associated with adenocarcinoma of the oesophagus (ACO). This definition would appear to have prevented the publication of follow-up studies of SIM neg CLO patients; therefore this supposition has not been tested.The current definition implies that there are 2 outcomes to the metaplasia of squamous epithelium to CLO, one stable and the other progressing to ACO. The epidemiology of these two differing types of metaplasia would be expected to differ. A study of 492 cases of BO, 320 males (248 SIM pos) 172 females (127 SIM pos), found, in a sub-group of 130 males (101 SIM pos) between ages 20-59 years and 144 females (107 SIM pos) between ages 20-79 years, a practically identical ±7.36% rise in the prevalence rates for each additional year of age for SIM pos CLO, SIM neg CLO and both types of CLO combined(p=0.92 for difference), with, however, a 20 year age shift between the age specific prevalence rate curves for the two sexes.
Conclusion: The similarities in the epidemiology of SIM pos and neg CLO do not support the supposition that they represented two different forms of metaplasia but suggest that they are 2 consecutive stages in the same metaplastic process.

The role of autofluorescence endoscopy for the detection of High Grade Intraepithelial Neoplasia (HGIN) in patients with Barrett Esophagus (BE).

M.A. Kara[1], M.E. Smits[1], W.D. Rosmolen[1], A.C. Bultje[2], F.J.W. ten Kate[3], P. Fockens[1], G.N.J. Tytgat[1], R.S. DaCosta[4], C. Streutker[5], N.E. Marcon[6], B.C. Wilson[4], J.J.G.H.M. Bergman[1]. Depts of Gastroenterology[1], Clinical Epidemiology and Biostatistics[2] and Pathology[3], Academic Medical Center Amsterdam, Dept of Medical Biophysics[4], Princes Magaret Hospital, Toronto, Canada, Dept of Pathology[5] and Center for Therapeutic Endoscopy & Endoscopic Oncology[6], St Michaels's Hospital, Toronto, Canada

Our aim was to study the role and mechanism of autofluorescence (AF) for the detection of HGIN in patients with BE. We conducted a randomized cross-over study comparing light induced fluorescence endoscopy (LIFE) with standard video endoscopy (SE). 50 BE patients underwent SE and LIFE in a randomized sequence with a 6-8 weeks interval. Two endoscopists were randomly assigned to each procedure. Targeted biopsies had a sensitivity for the diagnosis of patients with HGIN of 62% (8/13) for both techniques. The overall sensitivity (all biopsies) was 85% for SE and 69% for LIFE (p = 0.69). LIFE, therefore, did not improve the detection of HGIN in BE compared to SE.In another study, we used confocal fluorescence microscopy (CFM) for ex vivo characterization of epithelial AF in non-dysplastic BE (NDBE), low grade dysplasia (LGD) and HGIN. Frozen sections from 28 snap-frozen biopsies (from 10 pts with HGIN) were examined using CFM with blue light excitation and green and red emission. Pseudo-colored 8-bit digital images were taken from 42 NDBE, 40 LGD and 91 HGIN areas (homogenous histopathology). All tissues fluoresced mainly in the green spectrum. The main sources of AF in all tissues were the cytoplasm and lamina propria; nuclear and mucinous vacuole AF was negligible. There were no significant differences seen in AF intensity or microdistribution between NDBE, LGD and HGIN, except for quantitative differences secondary to morphological changes (e.g. mucosal thickening, increased nuclear/cytoplasmic ratio, increased Hb) in HGIN. The in vivo detectable differences in AF are therefore not caused by specific changes in endogenous epithelial fluorophores but probably reflect changes in tissue architecture and hemoglobin content that affect AF from submucosal collagen.These results gave new insight in the mechanism of AF in BE and helped overcome the technical shortcomings of earlier prototypes of fluorescence endoscopy (poor white light image (fiberoptic scope) and poor algorithms for AF imaging). A new prototype has been developed in which a high-resolution video endoscope is used together with an advanced algorithm for AF image acquisition and a narrow band imaging modality. Our first two studies using this new system have shown promising results.

Multi-Band Mucosectomy; a new and easy technique for widespread mucosal resection. A feasibility study in 17 patients with a Barrett esophagus

F.P. Peters[1], M.A. Kara[1], W.D. Rosmolen[1], F.J.W. ten Kate[2], K.K. Krishnadath[1], P. Fockens[1], J.J.G.H.M. Bergman[1]. Depts of Gastroenterology[1] and Pathology[2], Academic Medical Center, Amsterdam, Netherlands

Endoscopic resection (ER) of large mucosal lesions usually requires piece-meal resection. With the most widely used ER-cap technique, this is a laborious procedure which requires repetitive submucosal injections and the use of multiple snares. Multi-Band Mucosectomy (MBM) is a new technique that uses a modified variceal band ligator with multiple rubber bands attached to a standard variceal ligation cap (diameter 9 mm). For this technique, submucosal lifting is not required, prelooping of the snare is not necessary and multiple resections can be performed with one snare. Aim of this study was to evaluate the feasibility of MBM for widespread ER in patients with a Barrett esophagus (BE) containing high-grade intra-epithelial neoplasia (HGIN) or early cancer (EC).MBM was performed in 17 BE pts with HGIN (n=12) or EC (n=5). The duration of the procedure, the number of resections performed, and early complications were recorded. The size of the specimens was retrieved from histology reports. Data were compared retrospectively with 5 comparable ER-cap procedures, performed with a standard (12 mm) ER-cap.17 MBM procedures were performed in 15 pts. A median of 8 pieces were resected in a median time of 50 min in the MBM-procedures, versus 5 pieces in a median time of 50 min for the ER-cap group (p=0.01). Median diameter of the specimens was 17 mm for MBM-specimens and 20 mm for ER-cap-specimens (p=0.07), all resections involved the submucosa. Bleedings were seen in 2/17 (12%) MBM-procedures and in 1/5 (20%) cap-procedures, there were no perforations. Technical difficulties encountered during MBM-procedures included a decreased visibility due to the black bands covering the cap, and shifting of the wires into the field of view. Conclusions: MBM is an easy and rapid method for the resection of large areas of BE. Because submucosal lifting is not required and a single snare can be used for all resections, time and costs appear to be saved in comparison to the ER-cap-technique.

Topical administration of activated protein C reduced coagulation and improved survival in experimental polymicrobial peritonitis

S.Q. van Veen[1], A.K. van Vliet[1], T.M. van Gulik[1], M.A. Boermeester[1]. Dept of Surgery (Surgical Laboratory)[1], Academic Medical Center of the University of Amsterdam, The Netherlands

In peritonitis intra-abdominal fibrin entrapping bacteria prevents their elimination and is a nidus for bacterial growth and infection. Systemic use of the anticoagulant activated protein C (APC) has anti-inflammatory effects and improves survival in sepsis patients. There are no data on local efficacy of APC in abdominal sepsis. In this study in experimental polymicrobial peritonitis, effects of peritoneal lavage (PL) with APC on coagulation, fibrinolysis and survival were assessed simultaneously in abdominal, circulatory and pulmonary compartments.
In mice, 24 hours after cecal ligation and puncture (CLP) or sham operation, therapeutic PL was performed with APC (1.0 µg/ml) or saline. At 24, 48, 72 or 96 hours post-CLP (n=8/group/time point), PL fluid (PLF), blood and lungs were sampled. Bacterial load (BL) was measured, clotting time (CT) and thrombin-antithrombin complex (TAT) to assess coagulation, and tissue plasminogen activator (tPA), plasminogen activator inhibitor (PAI) and D-dimer to assess fibrinolysis. Survival was studied for 96 hours (n=22/goup).
After CLP, all parameters were increased at all time points in all compartments ($p<0.01$ vs sham). APC lavage reduced abdominal BL, and CT but not TAT levels in PLF and lungs to normal values compared to saline lavage ($p<0.05$). Also, plasma and PLF tPA levels reduced concomitant with increased PAI levels ($p<0.05$ vs saline). In contrast, pulmonary tPA levels increased concomitant with decreased PAI levels ($p<0.05$ vs saline). D-dimer reduced in PLF and lungs ($p<0.05$). Survival improved from 55% (saline) to 80% with APC lavage ($p=0.03$).
In this model of polymicrobial peritonitis, topical administration of APC reduced intra-abdominal bacterial load by inhibiting coagulation responses in both abdominal and pulmonary compartments concomitant with reduced abdominal fibrinolysis but increased pulmonary fibrinolysis. These compartmental balancing effects on coagulation and fibrinolysis translated into improved survival.

Contribution of the mucosal immune system to methotrexate induced intestinal damage *

B. de Koning[1,2], D. Lindenbergh-Kortleve[1], J. van Dieren[1], L. de Ruiter[1], T. Matsumoto[3], R. Pieters[2], H. Büller[1], A. Einerhand[1], J. Samsom[1], E. Nieuwenhuis[1]. Lab of Pediatrics, Div of Pediatric Gastro-enterology[1] and Pediatric Oncology[2], Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands, Dept of microbiology[3], Toho University School of Medicine, Tokyo, Japan

Methotrexate (MTX) induced intestinal damage is associated with increased exposure of the mucosal immune system to vast amounts of microbial stimuli. Because it is unclear how the mucosal immune system responds to this increased antigen load, and whether it contributes to mucositis, we have analyzed innate and adaptive immune responses in MTX induced mucositis.
To assess whether microbial stimuli contribute to the severity of MTX induced intestinal damage, LPS responsive and non-responsive mice were treated on day –1 and day 0 with 100- and 50 mg/kg MTX respectively. LPS responsive mice exhibited a more prolonged weight loss than non-responsive mice. Moreover, pre-treatment of WT mice with 5 µg LPS prior to MTX, resulted in a more profound weight loss and enhanced morphological damage, establishing a contributive role for luminal LPS to the severity of MTX induced mucositis. To elucidate the nature of the innate immune response upon MTX treatment, cytokine release by macrophages was measured after co-culture with MTX and LPS. Treatment with increasing concentrations of LPS, in the presence of MTX resulted in higher basal levels of TNF-α and actively induced IL-10 production. In vivo, this IL-10 release may have restricted the severity of mucositis as MTX treated IL-10-KO mice lost significantly more weight, and showed more severe morphological damage than WT controls. Not only the innate but also the adaptive intestinal immune system was affected by MTX as lamina propria lymphocytes, isolated from MTX-treated WT mice and re-stimulated in vitro produced significantly more TNF-α and IL-10 compared to cells from non-treated mice.
Conclusion: During MTX induced mucositis the enhanced release of microbial stimuli affects both the innate and the adaptive immune system leading to concomitant TNF-α and IL-10 release. Despite ongoing inflammation, IL-10 restricts excessive damage. These data may provide new targets in mucositis therapy.

CD4+ T lymphocytes mediate colitis induced by non-pathogenic Bacteroides vulgatus in HLA-B27 transgenic rats

F. Hoentjen[1,2], S.L. Tonkonogy[3], L.A. Dieleman[1,4], B. Feng Qian[1], B. Liu[1], J.D. Taurog[5], R. Balfour Sartor[1]. Depts of Gastroenterology and Hepatology, University of North Carolina[1], Chapel Hill, USA; Free University Medical Center[2], Amsterdam, The Netherlands; North Carolina State University[3], Raleigh, NC, USA; and University of Texas Southwestern Medical Center[5], TX, USA. Present address: Dept of Gastroenterology[4], University of Alberta, Edmonton, Canada

HLA-B27/β2 microglobulin transgenic rats spontaneously develop T cell-mediated colitis under specific pathogen free conditions but no inflammation in the germ-free state. Gnotobiotic HLA-B27 transgenic rats, but not non-transgenic littermates, develop colitis when monoassociated with *Bacteroides vulgatus* (*B. vulgatus*. It is not known whether T lymphocytes mediate disease. The aim of this study was to determine whether T cells are required for colitis to develop after HLA-B27 transgenic rats are monoassociated with *B. vulgatus*. Germ-free HLA-B27 transgenic *rnu/rnu* (athymic rats) and *rnu/+* rats (with normal T cell development) where monoassociated with *B. vulgatus* for 8-12 weeks. $CD4^+$ T cells ($0.5\text{-}1x10^7$) from mesenteric lymph nodes (MLN) of *B. vulgatus*-monoassociated *rnu/+* transgenic donor rats were transferred into *B. vulgatus*-monoassociated *rnu/rnu* transgenic recipients. Recipients were euthanized 7-9 weeks later and MLN cells were collected for measurement of *in vitro* cytokine secretion in response to *B. vulgatus* or *E. coli* lysates. Cecal and colonic tissue was collected for histologic evaluation of inflammation (scale 0-4), analysis of myeloperoxidase (MPO) and IL-1β production, and for interferon (IFN)-γ mRNA detection. *B. vulgatus*-monoassociated *rnu/+* but not *rnu/rnu* transgenic rats developed histologic evidence of mild colitis (1.4 ± 0.1 cecum, 1.0 ± 0.1 colon *rnu/+*). Cecal IL-1β, and MPO levels and colonic IFN-γ mRNA were significantly elevated compared to *rnu/rnu* transgenic rats. Disease was transferred by $CD4^+$ T cells into *rnu/rnu* transgenic rats, and only recipient MLN cells produced IFN-γ after *in vitro* stimulation with *B. vulgatus* (1.6 ± 0.2 ng/ml) but not *E. coli* lysates (0.03 ng/ml, $P<0.005$), while MLN cells from all rats secreted IL-10 in response to both bacterial lysates. Thus, T lymphocytes are necessary, and $CD4^+$ T lymphocytes are sufficient, for colitis to develop in gnotobiotic HLA-B27 transgenic rats colonized with non-pathogenic *B. vulgatus*.

Spontaneous development of colitis in mice deficient for Mucin 2 *

M. van der Sluis[1,2], B.A.E. de Koning[1], A. Velcich[3], I. van Seuningen[4], H.A. Büller[1], J. Dekker[1], I.B. Renes[2], A.W.C. Einerhand[1]. Paediatric Gastroenterology and Nutrition[1], Neonatology, Laboratory of Paediatrics[2], Erasmus MC-Sophia, Rotterdam, The Netherlands, Dept Oncology[3], Albert Einstein Cancer Center/ Montefiore Medical Centre, New York USA, Unité INSERM No560[4], Lille Cedex, France

Inflammatory bowel disease (IBD) is influenced by genetic, immunoregulatory and environmental factors. Mucin 2 (MUC2) is the major mucin of the mucus layer covering the colonic epithelium. Previous studies have shown that the expression of MUC2 is altered in IBD, and therefore might play a role in the onset and/or perpetuation of IBD. Our aim was to obtain insight in the role of MUC2 in epithelial barrier function, and its role in the pathogenesis of IBD. In this study we used Muc2 knockout mice. These mice were backcrossed onto a 129SV genetic background. Wild type (WT), heterozygous (HZ) and knock out (KO) littermates were scored weekly for weight, softness of the stool and appearance of occult faecal blood, to obtain a disease activity score (DAI). At age 5, 8, 12 and 16 weeks, groups of each 4 mice were sacrificed. Intestinal segments were collected for histological and biochemical analysis. The Muc2 knockout mice all showed clinical signs of colitis (KO DAI=4 ±1 vs. WT/ HZ DAI=0 at 5 weeks) aggravating in time (KO DAI=8±2 vs. WT/HZ=0 at 16 weeks) and incidentally rectal prolapses. Microscopic analysis of the distal colon showed mucosal thickening, increased proliferation, superficial erosions and distinct changes in goblet cell morphology. RT-PCR was used to monitor the RNA expression of other secretory mucins present in the gastrointestinal tract: Muc5AC, Muc5B and Muc6. Muc5AC, and -5B mRNAs were not detectable in the distal colon of both WT and KO mice. Muc6 was not expressed in WT colon. In the KO mice, however, Muc6 mRNA expression was present at 5 weeks of age, but expression declined as the mice matured. Conclusion: This study is the first to show that defects in Muc2, and therefore changes in the mucus composition in the intestine, cannot be compensated by other secretory mucins and spontaneously leads to colitis.

Immune stimulating effects of oat β-glucan on enterocytes *in vitro*.

J.D. Ramakers[1], J.J. Volman[1], G. Önning[2], M. Biörklund[2], R.P. Mensink[1], J. Plat[1]. Dept of Human Biology[1], Maastricht University, Maastricht, The Netherlands and Div. of Biomedical Nutrition[2], Lund University, Lund, Sweden

The oat derived fiber, β-glucan affects lipid and glucose metabolism, but also triggers inflammatory processes in macrophages. Immune modulating effects of oat β-glucan on enterocytes have however never been studied. Therefore, 24 hour pooled ileostomic contents from 6 subjects that had consumed in random order a diet with or without β-glucan (5 g) were freeze-dried. Fecal water was prepared and a concentration of 6.5 mg/mL was added to four intestinal cell lines (HT-29, T84, INT407 and differentiated Caco-2), which were stimulated for 16 hours with a mixture of interferon (IFN)-γ 100 U/mL), interleukin (IL)-1β (50 U/mL), and tumor necrosis factor (TNF)-α (10 ng/mL). As compared to placebo, β-glucan significantly increased IL-8 production in HT-29 (5.0%; p=0.046) and INT407 cells (22.0%; p=0.028). Intercellular adhesion molecule (ICAM)-1 expression increased in T84 (11.0%; p=0.028), INT407 (16.7%; p=0.043) and Caco-2 cells (20.4%; p=0.075). These immune stimulating effects were confirmed by inflammatory protein expression profiles, as determined with an antibody array.
We therefore conclude that, like in macrophages, oat β-glucan has immune stimulating effects on enterocytes, which suggest the presence of dectin-1 (the β-glucan receptor) on enterocytes. Since intraperitoneal infusion of oat β-glucan increases resistance to bacterial challenges in mice, our results could suggest that dietary oat β-glucan intake could have protective effects against pathogens. However functional consequences of increased β-glucan intake, as well as underlying mechanisms are subject of further studies.

The prebiotic combination inulin/oligofructose prevents colitis in HLA-B27 rats by immunomodulation and changes in intestinal microflora

F Hoentjen[1,2], G.W. Tannock[3], C.J. Mulder[2], L.A. Dieleman[4]. Dept of Medicine[1], University of North Carolina at Chapel Hill, USA, Dept of Gastroenterology[2], Free University Medical Center, Amsterdam, The Netherlands, Depts of Agriculture and Forestry[3] and Gastroenterology[4] University of Alberta, Edmonton, Canada

HLA-B27 transgenic rats develop spontaneous colitis when housed under specific pathogen-free conditions. Recently we showed that probiotic bacteria can prevent relapse of colitis in transgenic rats. The aim of this study was to investigate if oral prebiotics can prevent colitis in this model and to assess possible protective mechanisms. HLA-B27 transgenic rats received the prebiotic combination inulin/oligofructose in their drinking water, or not, prior to the development of clinically detectable colitis. After 7 weeks rats were killed, cecal tissue was collected for gross cecal scores (GCS), histologic inflammatory scores (scale 0-4), and mucosal cytokine measurement. Cecal and colonic content was collected for quantification of short-chain fatty acids (SCFA), and for bacterial analysis using PCR-denaturing gradient gel electrophoresis (PCR-DGGE) of bacterial DNA. Prebiotic treatment significantly decreased GCS (1.1±0.1 prebiotics, 3.4±0.1 untreated, $P<0.01$) and inflammatory histologic scores in the cecum (2.4±0.6 prebiotics, 3.9±0.1 untreated, $P<0.05$). The proinflammatory cecal IL-1β secretion was decreased (4.8±0.5 prebiotics, 9.2±1.4 ng/100 mg tissue untreated, $P<0.05$) whereas secretion of the immunoregulatory cytokine TGF-β was increased (154±40 prebiotics, 44±15 pg/100 mg tissue untreated, $P<0.05$) by prebiotic treatment. Prebiotics did not change luminal SCFA concentrations. PCR-DGGE showed that the prebiotics profoundly changed the intestinal microflora with an increase of luminal Bifidobacteria animalis.In summary, the prebiotic combination of inulin plus oligofructose partially prevented colitis in HLA-B27 transgenic rats. This correlated with an altered intestinal bacterial composition with increased luminal Bifidobacteria, and immunomodulation by decreased cecal IL-1β and increased TGF-β secretion. These results show promise for prebiotics as (adjuvant) maintenance therapy for chronic inflammatory bowel diseases.

Essential role for c-Raf in steroid insensitive Crohn's disease

M. Lowenberg[1], A. Verhaar[1], B. van den Blink[1], S. van Deventer[1], M. Peppelenbosch[2], D. Hommes[1,3]. Lab of Experimental Internal Medicine[1] and Dept of Gastroenterology[3], Academic Medical Center, Amsterdam, Dept of Cell Biology[2], University of Groningen, The Netherlands

Steroid resistance is a significant problem in the clinical management of Crohn's disease (CD). Recently, we tested the effect of a two week treatment with semapimod (CNI-1493) in twelve patients with steroid-refractory CD and observed dramatic clinical improvement, with remissions lasting up to one year. The aim of this study was to identify the cellular target underlying semapimod action. *In vitro* experiments using murine macrophages showed impaired MAPK phosphorylation and decreased cytokine production due to semapimod treatment. *In vitro* kinase assays revealed c-Raf inhibition as a direct molecular target of semapimod action. In addition, immunohistochemistry performed on paired colon biopsies obtained from CD patients (n=6) demonstrated high levels of phospho-MEK, the substrate of c-Raf. Strikingly, phospho-MEK levels were significantly decreased in patients with a good clinical response to semapimod, and no decrease in phospho-MEK expression was observed in a clinically non-responsive patient.
Conclusions: This study identifies c-Raf as the molecular target of semapimod action and suggests that decreased c-Raf activity correlates with clinical benefit in CD. Our observations indicate that c-Raf inhibitors are prime candidates for the treatment of severe CD.

Possible mechanism of action of tacrolimus in IBD: inhibition of NKT cell- and Intestinal epithelial cell- activation *

J.M. van Dieren[1], C.J. van der Woude[1], M.E.H. Lambers[2], E.J. Kuipers[1], E.E. Nieuwenhuis[3]. Dept of Gastroenterology & Hepatology[1], lab of pediatric Gastroenterology[2] and Dept of Pediatric Gastroenterology[3] Erasmus MC, University Medical Center Rotterdam, The Netherlands

Tacrolimus is a calcineurin inhibitor, which has been shown to be effective in the treatment of IBD. Inhibition of T cell activation has been suggested as the major mechanism of action of tacrolimus function. Other mucosal cells, however, have also been implicated in the pathogenesis of IBD, such as the intestinal epithelial cells (IEC), which are known to secrete many proinflammatory cytokines and chemokines. CD1d restricted T-cells have recently been found to be a major source of enhanced IL-13 production in human ulcerative colitis. The aim of this study was to determine whether tacrolimus exerts its effects through inhibition of activation of either CD1d restricted T-cells and/or IECs.
A CD1d restricted Natural Killer (NK) -T cell-line (DN32.D3) was stimulated by overnight incubation with a CD1d transfected intestinal epithelial cell-line (T84-d) that was pulsed with αGalactosylceramide (αGalCer). αGalCer is a glycolipid antigen that is known to activate NKT cells in a CD1d restricted fashion. Another intestinal epithelial cell-line (Caco-2) was stimulated by overnight incubation with peptidoglycan at 10μg/ml. Both in vitro assays were performed in the absence or presence of different concentrations of tacrolimus. NKT cell activation was determined by measurement of IL-2 production and Caco-2 stimulation by IL-8 production by means of ELISA. Tacrolimus caused a dose-dependent reduction of IL-2 production by NKT cells stimulated by an exogenous antigen (αGalCer) as presented by an IEC line. There was a total block of IL-2 production at tacrolimus concentrations of 1 μg/ml and higher. Caco-2 cell activation by peptidoglycan could be inhibited by tacrolimus; albeit only at high doses starting at 10 μg/ml. In conclusion, these data show that the inhibitory functions of tacrolimus can be extended to CD1d restricted NKT cells as well as IECs, which may explain the effectiveness of tacrolimus in IBD.

Turbo-probiotics as a tool for cell-based (mucosal) delivery of interleukin-10

H. Braat[1], L. Steidler[2], S. Neirynck[2], M.L. Kapsenberg[3], S.J.H. van Deventer[1], E.C. de Jong[3], D.W. Hommes[1]. Depts of Experimental Internal Medicine[1] and Cell Biology & Histology and Dermatology[3], Academic Medical Center, Amsterdam The Netherlands, Alimentary Pharmabiotic Centre[2], University College Cork, Cork Ireland

Introduction: The potent ability of dendritic cells (DCs) to instruct many different classes of lymphocytes and induce different types of T cell responses makes this cell-type an important target for several approaches of immuno-therapy, including long-term immunization, graft-versus-host disease, cancer and autoimmune disease. We describe a novel therapeutic strategy to induce suppressor immune responses via modulation of DC- and T cell function by genetically modified non-pathogenic Lactococcus lactis that expresses human IL-10 (LLIL-10). Methods: Monocyte-derived DCs were incubated with viable LL or LLIL-10, maturation factors (MF; IL-1β, TNF-α and LPS), mature DCs were cultured with naïve T cells to assess the nature of adaptive immune responses generated. Quiescent DC-primed T cells (test cells) were harvested and stained with PKH and pre-activated overnight with CD3 and CD28. The following day CD4+ T cells (responder cells) were labeled with CFSE and after 5 days the cellular content of CFSE responder cells was analyzed using flow-cytometry. Results: T cells generated by mature DCs exposed to LLIL-10 and MF showed profound ability to suppress the proliferation of responder T cells (60% inhibition compared to MF and 30% inhibition compared to LL and MF). The regulatory immune responses generated by LLIL-10 were dependent on full maturation of DCs as LLIL-10 generated DC without MF did not induce suppression. Furthermore, both DCs and T cells produced more IL-10 when DCs were matured with LLIL-10 than with LL, which was instrumental for the induction but not the function of the regulatory T cells.

CARD15 in inflammatory bowel disease and Crohn's disease phenotypes: an association study and pooled analysis

L.E. Oostenbrug[1], I.M. Nolte[2], E. Oosterom[2], G. van der Steege[2], G.J. te Meerman[3], H.M. van Dullemen[1], J.P.H. Drent[4], D.J. de Jong[4], K. van der Linde[5], P.L.M. Jansen[6], J.H. Kleibeuker[1]. Depts of Gastroenterology and Hepatology[1], Medical Biology[2] and Medical Genetics[3], University Medical Center Groningen, Dept of Gastroenterology and Hepatology[4], University Medical Center St. Radboud, Nijmegen, Dept of Gastroenterology and Hepatology[5], University Medical Center Erasmus, Rotterdam, Dept of Gastroenterology and Hepatology[6], Academic Medical Center, Amsterdam, The Netherlands

Background & Aims: Crohn's disease (CD) and ulcerative colitis (UC) are complex genetic disorders with multiple contributing genes. Three major polymorphisms of the CARD15 gene have been described to be associated with CD. We investigated the relation of CARD15 with IBD and CD phenotypic characteristics in a large Dutch cohort and performed a pooled analysis on IBD patients and CD phenotypic characteristics reported in association studies. Methods: We investigated 716 cases and 276 controls. A cohort of 369 CD patients was phenotyped. Individuals were genotyped for R702W, G908R and 1007fsinsC polymorphisms, as well as six microsatellite markers in and close to CARD15. Association analysis and the Haplotype Sharing Statistic were used to search for differences between patients and controls. In the pooled analysis raw data of 7201 IBD patients and 3720 controls from 20 CD genotype-phenotype studies were included. Results: The SNP association study showed CD susceptibility for R702W and 1007fsinsC. UC showed no association. Seven clinical characteristics showed association with 1007fsinsC: Age of onset <40 yrs, ileal localisation, ileocolonic localisation, penetrating disease, need for operation, anal involvement, and female gender. In the pooled analysis all three investigated polymorphisms showed association with CD at a 1% significance level. No association was found with UC. The frequency of the 1007fsinsC variant was significantly higher among CD patients with small bowel involvement, stricturing and penetrating behaviour and need for operation. The G908R variant was associated with small bowel involvement, stricturing behaviour and need for operation, the R702W variant was associated with small bowel involvement only. Conclusions: CARD15 is associated with CD and not with UC. All risk alleles are associated with small bowel involvement, the G908R and 1007fsinsC alleles also being associated with a complicated disease course.

NOD2/CARD15 modulates specific Toll-like receptor pathways for the induction of cytokine release

D.J. de Jong[1], M.G. Netea[2], B.J. Kullberg[2], T. Jansen[2], L. Jacobs[2], M. Kramer[3], A.H.J. Naber[1], J.P.H. Drenth[1], G.J. Adema[3], J.W.M. van der Meer[2]. Depts of Gastroenterology and Hepatology[1], Medicine[2] and Tumor Immunology[3], Radboud University Nijmegen Medical Center, The Netherlands

Variants in the NOD2/CARD15 gene are associated with Crohn's disease (CD). CARD15 plays a role in recognition of peptidoglycan (PGN) by the innate immune system. PGN also stimulated cytokine production via Toll-like receptor type 2 (TLR2). However, it is unclear if PGN stimulated cytokine release is primarily mediated by CARD15 or by TLR2. The aim of the present study was to demonstrate interactions between various Toll-like receptors and CARD15 in CD patients.Pro- and anti-inflammatory cell responses (TNF-alpha, IL-1beta and IL-10 production) were assessed after TLR specific microbial stimuli. Patients with CD, either bearing wild-type CARD15 or loss-of-function mutations of CARD15 were studied. We demonstrate that CARD15 is required for recognition of PGN, which leads to strong synergistic effects on TLR2-mediated production of both pro- and anti-inflammatory cytokines. Furthermore, in patients bearing loss-of-function mutations, depression of pro- inflammatory response is overwhelmed by disrupted anti-inflammatory response. In addition to the synergy with TLR2 effects, CARD15 is also a modulator of signals transmitted through TLR4 and TLR3, but not through TLR5, TLR9 or TLR7. In conclusion, after TLR2 specific stimuli, defective IL-10 production may lead to overwhelming inflammation due to defective Th1 response as evidenced by low IL-12 production, in patients bearing loss-of-function mutations of CARD15. The interaction between CARD15 and specific TLR pathways may represent an important modulatory mechanism of innate immune responses in CD patients.

Functional Consequences of NOD2 Deficiency in Crohn`s Disease Patients Peripheral Blood Monocytes Derived Dendritic Cells

Z. Zelinkova[1], F. de Kort[1], I. Pronk[1], A. te Velde[1], M. Peppelenbosch[1], S. van Deventer[1], D. Hommes[2]. Lab of Experimental Internal Medicine[1] and Dept of Gastroenterology[2], Academic Medical Center Amsterdam, The Netherlands

Mutations in the gene encoding nucleotide-binding oligomerization domain 2 (NOD2) are associated with increased risk of developing Crohn`s disease (CD). NOD2 is a receptor for a component of bacterial peptidoglycan (PGN), muramyl dipeptide (MDP). Recently, it has been suggested that NOD2 deficiency in mice macrophages may lead to a defective regulation of Toll-like receptor 2 (TLR2)-driven Th1 response. To test the relevance for a human situation, we assessed functional consequences of NOD2 deficiency in ex vivo cultured antigen presenting cells from Crohn`s disease patients with double dosis mutation and wild type healthy controls. Peripheral blood monocytes derived immature dendritic cells (DC`s) from patients and controls have been matured with cytokines coctail and stimulated with a TLR2 ligand (PGN) and a NOD2 ligand (MDP), respectively. Cytokine production upon stimulation was measured in supernatants by cytometric beads array and maturation status of DC`s has been assessed by the means of CD83 expression by flow cytometry.A lower percentage of fully mature DC`s was found in healthy controls compared with patients. This was consistent with the finding of IL-12 production by patients whereas controls DC`s IL-12 production was undetectable. In patients, PGN and MDP stimulated additional IL-12 production compared to baseline mature DC`s while no IL-12 production upon stimulation has been observed in healthy controls. On the other hand, more than 10 fold increase of IL-10 production was observed in PGN stimulated cells from controls while only slight increase in IL-10 production was noticed in patients. No effect on IL-10 production has been found with MDP stimulation in both groups.Our results provide an explanation of NOD2 defect mechanism in Crohn`s disease. This may be associated with CD through an insufficient inhibition of proinflammatory cytokines production upon Toll-like receptor-driven activation together with impaired regulatory cytokines production.

Barrett Esophagus (BE) with High-Grade intraepithelial neoplasia (HGIN) and/or Early Cancer (EC): Stepwise Radical Endoscopic Resection (SRER) for Complete Removal of the BE Is Safe and Effective

F.P. Peters[1], M.A. Kara[1], W.D. Rosmolen[1], F.J.W. ten Kate[2], K.K. Krishnadath[1], J.J.B. van Lanschot[3], P. Fockens[1], J.J.G.H.M. Bergman[1]. Depts of Gastroenterology[1], Pathology[2], and Surgery[3], Academic Medical Center, Amsterdam, The Netherlands

Endoscopic resection in BE is mostly used to resect focal HGIN/EC. These ER's are often irradical and many pts develop metachronous lesions elsewhere in the BE during FU. Our aim was to prospectively evaluate the safety and efficacy of SRER in pts with HGIN/EC in a BE.
After work-up with high-resolution endoscopy (HRE), video-autofluorescence imaging (AFI), narrow-band imaging (NBI) and EUS, and review of all biopsies by an expert pathologist, pts with HGIN/EC in a BE ≤ 5 cm, without signs of submucosal infiltration and lymph node metastases were included. Pts first underwent a diagnostic ER of the most suspicious lesion to evaluate infiltration depth, followed by SRER with intervals of 6 weeks. In all ER's the cap-technique was used. FU endoscopies (with lugol-staining, jumbo biopsies) were scheduled every 3 months, with EUS after 6 and 12 months.
Forty-one consecutive pts (33 m/8 f, mean age 65, median length BE 4 cm) were included. Complete removal was achieved in 26 pts (median 3 SRER's). Therapy was discontinued in 2 pts due to unrelated co-morbidity, 13 are still under treatment. Complications occurred in 12/87 procedures (14%): 11 bleedings (all treated endoscopically with no drop in Hb or need for blood transfusions) and 1 asymptomatic perforation treated conservatively. Stenosis occurred in 5/26 (19%) pts, requiring a median of 3 dilatations. Histopathology of ER-specimens revealed: HGIN in 16 and EC in 14 pts. In all specimens, deeper resection margins were free. Although revision of pre-treatment biopsies confirmed HGIN/EC, 11 pts did not have HGIN/EC in the ER-specimens.
During a median FU of 7 months none of the pts had signs of residual BE or buried Barrett in any of the biopsies and no signs of lymph node metastasis on EUS.
Conclusions: SRER is safe and effective for selected pts with HGIN/EC in a BE. SRER provides optimal histopathological diagnosis and may reduce the number of recurrences, since all the mucosa at risk is effectively removed.

Endoscopic ultrasonography (EUS) for staging of esophageal cancer in a non-expert EUS center

E.P.M. van Vliet[1], M.J.C. Eijkemans[2], J.W. Poley[1], E.W. Steyerberg[2], E.J. Kuipers[1], P.D. Siersema[1]. Depts of Gastroenterology[1] and Public Health[2], Erasmus MC/University Medical Center Rotterdam, The Netherlands

It is not known whether the volume of endoscopic ultrasound (EUS) performed affects the results of esophageal cancer staging. We compared EUS in the evaluation of T-stage, and regional (N-stage) and celiac (M-stage) lymph nodes in a center where <50 EUS/endoscopist/yr were performed, with reported results from 5 expert centers (>50 EUS).From 1994 to 2003, 244 patients underwent EUS, without fine-needle aspiration (FNA) or measures to pass a stenotic tumor, and with post-operative stage as gold standard. EUS was performed by 4 endoscopists in the non-expert center, without difference over time or between endoscopists. In 71 (29%) patients, the tumor could not be passed and EUS staging was incomplete. In expert centers, 670 patients underwent EUS, if needed with dilation or a small-caliber probe, and with post-operative stage and/or FNA as gold standard.Sensitivity in the non-expert EUS center to distinguish T3 from other T-stages was 85% (75/88) and 79% (49/62), with a specificity of 57% (48/85) and 11% (1/9), with or without passage of EUS probe, resp. In expert centers, higher sensitivities (88-94%) and specificities (75-90%) were reported. Sensitivity in the non-expert center for N-stage was 45% (42/94) and 32% (14/44), with a specificity of 75% (58/77) and 91% (19/21), with or without passage, resp. In expert centers, higher sensitivities (63-89%) and comparable specificities (75-82%) were reported. Sensitivity in the non-expert center for M-stage was 19% (3/16) and 11% (1/9), with a specificity of 99% (154/155) and 100% (56/56), with or without passage, resp. In expert centers, higher sensitivities (72-83%) and comparable specificities (85-100%) were reported.
Conclusions: The results of EUS performed in a non-expert EUS center compared unfavorably with those obtained in expert centers. Our results suggest that preoperative staging by EUS, preferably with FNA and the use of a small-caliber EUS probe, should be performed by experienced endoscopists (>50 EUS/yr).

Detection of severe neoplasia in Barrett's esophagus using auto-fluorescence endoscopy

J. Haringsma, J.W. Poley, I.M. Kerkhof, H. van Dekken, P. Blok, E.J. Kuipers. Dept of Gasroenterology[1] and Pathology[2], Erasmus MC University Medical Center, Rotterdam, The Netherlands

Barrett`s esophagus (BE) carries an increased risk for developing adenocarcinoma. As early neoplasia is often not visible with standard endoscopy (SE), surveillance programs rely heavily on random-biopsy sampling. Fluorescence endoscopy (FE) is a technique that can be used to visualize areas of intraepithelial neoplasie at endoscopy for targeted biopsy sampling or Endoscopic Mucosal Resection (EMR). A novel FE system using a fluorescence-reflectance ratio (Onco-Life, Xillix, Vancouver, BC Canada) is developed for real-time detection of adenomas in the colon. Ratio settings were slightly adapted to compensate for differences in background fluorescence in BE. The purpose of this pilot study is to prove the feasibility of neoplasia detection in BE using this system. Methods: Patients referred with suspected neoplasia in BE were screened subsequently with SE and FE. The segment of BE was carefully inspected and documented. All lesions were immediately judged to be either dysplastic or non-dysplastic using both techniques. EMR was performed, or targeted biopsies taken of each endoscopic or fluorescence abnormality. Results were compared to the pathology results. Results: Eighteen BE patients with suspected neoplasia were included: 4 patients had high-grade dysplasia (Vienna 4-1) and 8 intramucosal carcinoma (Vienna 4-4). Two patients were previously treated with photodynamic therapy for ablation of neoplasia. With FE 11 of 13 severe neosplasias were visualized (sensitivity 85%, specificity 57%), with SE 5 of 13 could be detected (sensitivity 38%, specificity 86%) (p=0.04).
Conclusions: In a selected group of patients fluorescence endoscopy significantly improves detection of intraepithelial neoplasia over standard endoscopy. Fluoescence imaging enables screening of large surface areas of metaplastic mucosa, and targeted treatment or biopsy sampling of severe neoplasia.

Intraluminal oxygen prevents mucosal ischemic damage in a new model of complete local small bowel ischemia in pigs

P.B.F. Mensink[1], C. Kruse[2], J.J. Kolkman[1], B. Reszel[3], U. Holscher[3], A. de Weerd[4], G Knichwitz[2]. Dept of Gastroenterology[1], Medical Spectrum Twente, The Netherlands, Dept of Anesthesiology[2], Universital Hospital Muenster, Germany, University of Apllied Sciences[3], Steinfurt, Germany, Medical Measurement Systems[4], Enschede, The Netherlands

Introduction Microvascular ischemia of the gastrointestinal tract is an important, and difficult to treat disorder. It is an important mechanism underlying e.g. radiation proctitis, Crohn's disease and anastomotic leakage after esophageal and colorectal resections. In the latter, it is the main contributor to anastomic leakage, morbidity and mortality. We explored a new approach by applying intraluminal oxygen in an animal model with complete local GI-ischemia.MethodsIn large pigs, a 70 cm small bowel loop was isolated, vessels were ligated and 2 tubes placed intraluminally at both ends; over these tubes tight ligatures were placed, thereby interrupting the collateral intramural vessels, creating complete small bowel ischemia. Complete hemodynamic monitoring, as well as blood gas sampling, was performed. Oxygen (5 ml/min) was administered intraluminally in the middle part of the ischemic loop, via a multi channel catheter connected to a prototype applicator. Mucosal blood flow and oxygen saturation were measured. Complete ischemia was maintained for 2 hr. Afterwards, transmural tissue samples were taken for histopathology from the ischemic loop (in the middle part, 10, 20 and 30 cm proximal and distal). Mucosal damage was graded according to the Chiu classification (grade 0 to 4). Results Six pigs received no oxygen (sham) and 6 pigs received oxygen (treatment). Hemodynamic parameters remained stable and did not differ between both groups; no evidence of systemic inflammatory response was found. In both groups no mucosal blood flow was detectable. The sham-group showed severe ischemia, the treated group showed macroscopically almost normal bowel with microscopically preserved mucosa centrally (table; histopathology scores (SD)).
Conclusions: We developed a new animal model of a complete, segmental small bowel ischemia. With a prototype applicator, intraluminal oxygen maintained mucosal integrity and viability despite complete cessation of blood flow. This seems an attractive approach in clinical situations with local mucosal ischemia, e.g. anastomotic wound healing, and deserves further investigation.

Genome wide response to starvation in the mouse small intestine

M. Sokolovic[1], T. Hakvoort[1], D. Wehkamp[2], L. Gilhuijs-Pederson[2], R. van Haaften[3], C. Evelo[3], A. van Kampen[2], W.H. Lamers[1]. AMC Liver Centre[1] and Bioinformatics Laboratory[2], Academic Medical Centre, Amsterdam; BiGCaT Bioinformatics[3], University of Maastricht, The Netherlands

The goal of the study was to acquire an unbiased representation of the complexity of the adaptive response of the gut to food deprivation, being the most extreme and most stressful condition in terms of food-gut relationship. Mice fed ad libitum or fasted 12, 24 and 72 hours were used to estimate the change in expression profile as a result of short and prolonged fasting. Microscopic analysis of the intestines did not reveal regressive changes, such as atrophy of the villi, even after long-term starvation. Abundance of the intestinal mRNAs, isolated using CsCl-gradient centrifugation, was estimated using the Agilent's Mouse Development Oligo Microarray (n=3 per group). Following a Quantile normalization procedure 1513, 1302 and 3031 genes (after 12, 24 and 72h of starvation, respectively) appeared after ANOVA analysis to differ significantly from fed controls, displaying a change greater than 1.4 fold. Validation of the data using RT-PCR on a subset of the genes showed correspondence with the data obtained from the microarray, with the best correlation for the abundant genes. Pathway analysis of the data using GenMAPP software revealed a marked difference in the pathways that figured prominently during the initial and the prolonged phases of fasting. At all time points, genes coding for components in all five complexes of the electron transport chain were downregulated. During the first 24 hours of fasting, a strong change in amino-acid metabolizing and processing pathways was detected, including virtually all amino acids and changing towards the preservation of amino acids. Genes aimed towards "survival" (cell-cycle regulation, proteasome degradation and apoptosis) only changed late. The same holds for energy metabolism, including downregulation of pentose phosphate pathway and the TCA cycle. These synchronized changes reveal that the adaptive hunger-response of the intestine changes with the duration of fasting and suggest that the response is highly coordinated.This work was supported by the Dutch Ministry of Economic Affairs through the Innovative Oriented Research Program on Genomics (IOP Genomics: IGE01016).

A Prospective Study Comparing Video Capsule Endoscopy Followed by Double Balloon Enteroscopy for Suspected Small Bowel Disease

M. Hadithi, G. Dimitri N. Heine, M.A.J.M. Jacobs, A.A. van Bodegraven, C.J. Mulder. Dept of Gastroenterology, VU University Medical Center, Amsterdam, The Netherlands

Background & Aims: This study was undertaken to prospectively compare the clinical outcomes of the wireless capsule endoscopy followed by double-balloon enteroscopy. Methods: Fifty consecutive patients with suspected small bowel disease were evaluated. The results of the Given M2A wireless video capsule (Given Imaging Ltd., Yoqneam, Israel) endoscopy and the double-balloon enteroscopy (Fuji Photo Optical Incorporated Company) were compared (17 males, and 33 females; mean age 60.5 yr; range, 19–86 yr; mean BMI (±SD) 25 ± 3.9). Results: Capsule endoscopy was normal in 11 patients, showing positive findings in the remaining 39 patients. Average time to evaluate each video was 76 min (45 110) minutes. Double-balloon enteroscopy, performed in an average of 106 ± 36 minutes (range 45-195) minutes, was normal in 17 and showed positive findings in the remaining 33 patients. Biopsies, argon plasma coagulation, tattooing and polypectomy were feasible when indicated in 42 (84%). Two patients reported post interventional abdominal pain requiring hospital admission that resolved conservatively within less than three days. The VCE was considered diagnostic in 40 of 50 (80%) patients, suspicious in 2 (4%) and non diagnostic in 8 (16%) patients. The DBE was considered diagnostic in 37 (72%), suspicious in 1 (2%), and non diagnostic in 12 (24%) patients. Both examinations were well tolerated, but capsule endoscopy was better accepted by patients. Conclusions: Both the video capsule endoscopy and double-balloon enteroscopy have high diagnostic yield. Although the visual diagnostic yield of video capsule is superior, our results indicate that the procedures are complementary; an initial imaging study employing video capsule endoscopy can be followed by interventional double-balloon enteroscopy.

Double balloon enteroscopy in Peutz Jeghers disease
First experience with a new diagnostic and therapeutic tool

G.D.N. Heine[1], M.H.A. Hadithi[1], M.J.M. Groenen[2], E.J. Kuipers[2], A.A. van Bodegraven[1], M.A.J.M. Jacobs[1] and C.J.J. Mulder[1]. Depts of Gastroenterology and Hepatology, VU University Medical Center[1], Amsterdam and Erasmus MC University Medical Center Rotterdam[2], The Netherlands

Although Peutz – Jeghers polyps are not true neoplasms, malignant degeneration in adenoumatous epithelium occurs in colon, small intestine and stomach. The advent of double balloon endoscopy (DBE, Fujinon Japan) allows identification and assessment of polyps in jejunum and ileum by full length endoscopy and enables validation of conventional enteroclysis. Moreover polyps may be removed by snare loops. The results of a first series of DBE enteroscopies in Peutz Jeghers' cases are presented. A preliminary comparison between efficacy of imaging techniques and endoscopy is made. Double balloon enteroscopy was performed in 125 patients. Eight patients of this series were known Peutz Jeghers cases, 1 patient was newly diagnosed. The other indications comprised obstruction in 4 and surveillance in 4 patients. The cecum was not reached in all patients after average procedure duration of 94 minutes, a duration intentionally limited to approx 90 minutes because of patient tolerability. After tattooing enteroscopy was completed ab-anally in 3 out of 9, interobserver blinded MRI enteroclysis was performed before DBE. The average number of obstructive polyps found were 4 in the obstructive and 2 in the surveillance group, at an average insertion length of Treiz + 320 cm. Apart from intra-abdominal abscesses requiring hospitalization in this patient, there were no complications. Histology showed high-grade dysplasia in 1 polyp in the surveillance group and low-grade dysplasia in all other polyps. Conventional enteroclysis was performed in 4 cases, all obstructive disease: of 16 polyps 7 were not identified. MRI enteroclysis was performed in two obstructive cases, and showed to be equally effecttive at diagnosing polyps.
Conclusions: Double balloon enteroscopy is a safe technique both for treatment and for surveillance in Peutz Jeghers disease. The diagnostic yield seems to be superior to conventional enteroclysis. As such its role as a surveillance tool seems promising

FDG-PET detects malignant degeneration of duodenal adenomas in familial adenomatosis polyposis patients and can change clinical management

M.C.A. van Kouwen[1], H.J. van Krieken[2], H. van Goor[3], W.J.G. Oyen[4], J.P.H. Drenth[1], F.M. Nagengast[1]. DeptS of Gastroenterology and Hepatology[1], Pathology[2], Surgery[3] and Nuclear Medicine[4], Radboud University Nijmegen Medical Centre, The Netherlands

Familial adenomatous polyposis (FAP) is an autosomal dominant inherited disorder, is characterized by the development of multiple colonic and duodenal adenomatous polyps, and carries a high risk of malignant transformation. Malignant degeneration of duodenal adenomas is difficult to detect and current clinical practice is to identify high-risk patients by gastroduodenoscopy, aimed to intervene before cancer develops. The effectiveness of this strategy is unclear, and we speculated that 2-(18F)-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) might be able to detect duodenal cancer in FAP. To this end, we investigated the role of FDG-PET in the clinical management of advanced duodenal adenomas in FAPWhole body FDG-PET was performed in 24 FAP patients with duodenal adenomas. Six patients had advanced duodenal adenomas (Spigelman IV). A positive scan was defined as focal FDG accumulation at any body site. Pathological FDG accumulation was absent in 19 of 24 FAP patients. All 6 patients with Spigelman IV duodenal adenomas were negative; 2 of these underwent a duodenectomy but pathological examination of the resected specimen did not reveal duodenal cancer. In 5 patients FDG-PET revealed significant uptake: duodenum (2); lower abdomen (1); lung (1). These hotspots correlated with duodenal cancer (2), abdominal metastasis of a pouch carcinoma (1), and sclerosing hemangioma of the lung (1). We failed to make a histopathological diagnosis in a single patient with multiple intra-abdominal FDG spots. None of the patients from the FDG-PET negative group developed cancer during follow-up (mean 2.8 years).FDG-PET detected all the cancers present; in the group patients with a negative FDG-PET none of the patients developed duodenal cancer. This suggests that a positive FDG-PET in FAP patients changes clinical management in these patients and should lead to further examinations, even if this necessitates surgery to rule out cancer. In patients with a negative FDG-PET a more lenient approach seems justified.

Tumour progression in colorectal cancer: array-CGH analysis of the 8q22 q23, 13q21-q31 and 20q amplicons

B. Carvalho[1], C. Postma[1], S. Mongera[1], M.A.J.A. Hermsen[2], B. Ylstra[3], G.A.Meijer[1]. Depts of Pathology[1] and Microarray core facility[3], VU University Medical Center, Amsterdam, The Netherlands and IUOPA[2] - Hospital central de Asturias, Oviedo, Spain

Introduction Colorectal cancer is the second leading cause of cancer death in the western world, with over 4200 deaths per year in The Netherlands. Colorectal cancer arise from adenomas, which in only 5% of cases ever progress to carcinomas.We showed by CGH, that gains at chromosomes 8q22-q23, 13q21-q31 and 20q13 are associated with progression of colorectal adenomas to carcinomas. We aimed to further delimit the boundaries of the gained 8q, 13q and 20q regions, in order to identify putative oncogenes in these regions, involved in tumour progression. Materials and methodsIn total, 32 paired samples from the adenoma and carcinoma compartments of malignant polyps were analysed by array-CGH, using a whole-genome BAC-array with an average resolution of 1Mb and a high resolution at 8q22-q23, 13q21-q31 and 20q13 regions. Results In addition to gains and losses that had previously been detected by classical CGH, array CGH revealed several other chromosomal alterations. In most cases, the adenoma and carcinoma parts of malignant polyps showed the same pattern of aberrations while in some cases carcinomas presented additional aberrations. Within the 8q, 13q and 20q regions we were able to delimit small regions of amplification (1-2 Mb). These regions contain several candidate oncogenes, like PTP4A3 (8q) and BCL2L1 (20q), which were also shown to be amplified in colon by multiplex ligation-dependent probe amplification (MLPA).
Conclusion Array-CGH allowed further restriction of the 8q, 13q and 20q gains associated with colorectal adenoma-to-carcinoma progression. Moreover, we identified small regions of amplification not previously detected by classical CGH, which may harbour the genes involved in colon cancer progression.

The secondary bile acid deoxycholic acid induces differential expression of chemokines in the progression of Barrett's esophagus to adenocarcinoma

D.A. Bax, L.M.G. Moons, E.J. Kuipers, F. Kariem, J. Haringsma, A.H.M. van Vliet, J.G. Kusters, P.D. Siersema. Dept of Gastroenterology and Hepatology, Erasmus MC - University Medical Center Rotterdam, The Netherlands

Chemokines are chemotactic cytokines predominantly produced by epithelial cells, which control leukocyte trafficking during tissue homeostasis as well as during inflammation and neoplastic growth. The aim of this study was to determine whether there are differences in chemokine expression in biopsy samples from patients with reflux esophagitis (RE), Barrett's esophagus (BE) and esophageal adeno-carcinoma (EAC), and whether these differences are induced by the secondary bile acid deoxycholic acid (DCA). Chemokine transcription was determined in 89 biopsy specimens from squamous epithelium from patients with BE (SQ, n=21) and RE (n=11), non-dysplastic BE (ND, n=17), BE with low-grade dysplasia (LGD, n=10), BE with high-grade dysplasia (HGD, n=14), and EAC (n=16), obtained from 37 patients with BE and 11 patients with RE. Transcription of the chemokines MCP-1, RANTES, MIP3α, MEC, and IL8 was assessed by semi-quantitative RT-PCR on RNA isolated from biopsy samples and OE21 cells. The effect of DCA was established by exposing OE21 cells to this bile acid. Transcription of MIP3α and MEC was significantly higher in ND compared to SQ and RE ($p<0.001$). MCP-1 transcription was increased in RE and ND compared to SQ ($p<0.01$). MIP3α mRNA levels increased with progressive histological stages (from SQ to RE, BE, LGD and HGD) and this was significant when EAC was compared to ND ($p<0.01$). In vitro incubation of OE21 cells with DCA resulted in increased MEC, MIP3α, and IL8, but not RANTES mRNA levels ($p<0.05$), partially mimicking the transcriptional patterns observed in the biopsies.
Conclusions: BE is associated with increased mRNA levels of MEC, MIP3α and MCP-1. Moreover, the development of EAC was associated with even higher levels of MIP3α. The induction of MIP3α by the bile acid DCA and its increased expression during the metaplasia-dysplasia-adenocarcinoma sequence suggests that this chemokine may play a key role in the malignant progression of BE.

Indomethacin disrupts protective effect of phosphatidylcholine against bile salt-induced ileal mucosa injury

N.G. Venneman[1], M. Petruzzelli[1,2], J.E. van Dijk[3], A. Verheem[1], L.M.A. Akkermans[1], A.B.A. Kroese[1,4], K.J. van Erpecum[1]. Gastrointestinal Research Unit[1], Depts of Gastroenterology and Surgery, and Dept of Medical Physiology[4], University Medical Center Utrecht, Utrecht, The Netherlands; Section of Internal Medicine[2], Dept of Internal and Public Medicine, University of Bari Medical School, Bari, Italy, Dept of Pathobiology, Division Pathology[3], Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands

Gastrointestinal ulcers are frequently found during treatment with NSAIDs. Since these side effects also occur in cylcooxygenase-1 (COX-1) knockout mice, they appear in part COX-independent, and possibly related to cytotoxicity of intestinal bile salts. We therefore investigated effects of indomethacin, with or without hydrophobic taurodeoxycholate (TDC) and protective egg-yolk phosphatidylcholine (PC) on small intestinal mucosa. Rat ileal mucosa was incubated during 30 min. in Ussing chambers with control-buffer, TDC, indomethacin, TDC-indomethacin, TDC-PC, or TDC-PC-indomethacin. Electrical resistance and trans-mucosal Na-fluorescein flux were determined as indicators of trans-mucosal permeability, and ileal histopathology was evaluated to quantify extent of mucosal injury. In CaCo-2 cells, LDH-release as measure of cytotoxicity was determined after incubation with various model systems. We found that electrical resistance decreased mostly, transmucosal Na-fluorescein flux was highest, and extent of mucosa injury by histological examination was most pronounced in case of TDC-indomethacin incubation (TDC-indomethacin > TDC > indomethacin, control-buffer). Indomethacin alone did not have any effect. PC protected against cytotoxic effects of bile salts, but only in absence of indomethacin ($P < 0.05$ for all parameters). Also, in CaCo2-cells, LDH-release was strongest in case of TDC-indomethacin incubation ($P < 0.001$), whereas indomethacin alone did not have any effect.
Conclusions: Indomethacin disrupts protective effects of phosphatidyl-choline against bile salt-induced ileal mucosa injury. These findings may be relevant for small intestinal ulcers caused by NSAIDs.

Efficient detection of genetic abnormalities in Barrett's esophagus patients by automated analysis of DNA FISH on brush cytology specimens

A. Rygiel[1], J.J.G.H.M. Bergman[2] J.W.P.M van Baal[1], F. Milano[1], M.P Peppelenbosh[3], K. K. Krishnadath[2]. Lab of Experimental Internal Medicine[1] and Dept of Gastroenterology and Hepatology[2], Academic Medical Center Amsterdam and Dept of cell biology[3], Rijks Universiteit Groningen, The Netherlands

Background: Barrett's esophagus (BE) is condition associated with an increased risk for developing adenocarcinoma. The progression of BE to cancer is a gradual process that is characterized by the accumulation of several genetic abnormalities. These abnormalities can be detected in cytology specimens by using DNA Fluorescent In Situ Hybridization (FISH). Manual scoring of FISH results is time consuming and labor intensive. AIM: The main goal of this study is to validate an automated FISH spot counting system for reproducible assessment of a panel of genetic markers by DNA FISH on brush cytology specimens for identification of BE patients at greater risk for progression towards adenocarcinoma. Material and methods: Multi-color FISH using a panel of 6 different DNA probes for chromosome 9,17 and Y and telomeric probes for 9(p16), 17q(Her2/neu)and 17p(p53)was applied on 60 brush cytology specimens separately taken from normal squamous epithelium (n=20)and Barrett mucosa (n=40). Results was analyzed through manual scoring and compared to analysis with the novel ARIOL spot counting software (Applied Imaging, Newcastle UK). Results: Manual analysis of FISH results showed genetic abnormalities in 50% of cases. The most common genetic changes were allelic losses of p16, p53 and loss of Y chromosome. These three alterations had a frequency of 37%, 10 % and 10% respectively. Also amplification of Her2/neu was observed in lower frequency. Subsequently these cases where analyzed by the automated microscope and ARIOL Spot counting software. On average, a high concordance of 95% to 98% was achieved between manual and automated analysis when scorning for the normal squamous cytology samples (controls.In the Barrett samples a concordance of 90% to 95% was found. Importantly, reviewing of discordant cases showed that the ARIOL software allowed detection of abnormalities which were missed when scoring manually. Our first analysis of the ARIOL spot counting software shows that automated analysis of FISH on cytology samples of BE patients is highly efficient and reproducible and enables us to improve surveillance of BE patients through analysis of genetic markers.

Fine-mapping of the coeliac disease linkage region on chromosome 19p13 reveals a new player in the field

A.J. Monsuur, I. Lavrijsen, A. Zhernakova, L. Franke, C. Wijmenga. Complex Genetics Section, DBG-Department of Medical Genetics, University Medical Center Utrecht, The Netherlands

Coeliac disease (CD) is a complex genetic disorder. Besides the environmental factor gluten and the HLA-DQ2 and 8 proteins, other unknown genetic factors are involved. Several genome-wide screens have been performed to locate the regions with genes involved in CD. In the Dutch population this has led to the discovery of two susceptibility regions, 6q21-22 and 19p13 (CELIAC4). The region on 19p13 is only limited to 3.5 Mb, but since it is a region with a high density of genes, it still contains 92 candidate genes. We set out to fine-map this region with microsatellite markers and single nucleotide polymorphisms (SNPs) to search for association between genes and CD. We started with a cohort of 216 cases and 216 controls and expanded this to 311 cases and 540 controls. Association testing using microsatellite markers has revealed a small region of interest of around 450 kb. Further fine-mapping with SNP shows association in a 150 kb region, encompassing a limited number of genes. Adding more SNPs led to the discovery of MYO9B as the gene on 19p13 most strongly associated to CD. This gene, which is a single-headed motor myosin, shows association in its 3' part. This part of the gene contains the most interesting domains, which also differentiate the role of this myosin from the other family members. The Rho-Gap and Dag-Pe domains indicate that this gene is involved in signal transduction. We are now elucidating the specific role of this gene in signal transduction and trying to incorporate it in our models for CD.

The transcriptomes of Barrett's esophagus and normal esophageal squamous epithelium by Serial Analysis of Gene Expression (SAGE)

J.W.P.M. van Baal[1], K.K. Wang[2], F. Milano[1], A.M. Rygiel[1], J.J.G.H.M. Bergman[3], S.J.H. van Deventer[1], M.P. Peppelenbosch[4], K.K. Krishnadath[3]. Depts of Experimental Internal Medicine[1] and Gastroenterology & Hepatology[3], Academic Medical Center, Amsterdam, The Netherlands, Dept of Gastroenterology and Hepathology[2], Mayo foundation, Rochester, USA, and Dept of Cell Biology[4], Rijksuniversiteit Groningen, Groningen, The Netherlands

Background: Barrett's esophagus (BE) is a premalignant condition in which the normal squamous epithelium of the distal esophagus is replaced by columnar lined epithelium. Little is known about the molecular and cellular responses involved in the transition of esophageal squamous epithelium into columnar epithelium. AIM: To understand the transition from squamous epithelium into metaplastic columnar epithelium we performed objective, quantitative analyses and comparison of the transcriptomes of Barrett's esophagus and normal esophageal epithelium. Material and methods: Serial analysis of gene expression (SAGE) allows a rapid, quantitative and simultaneous analysis of thousands of genetic transcripts from a tissue sample. SAGE was used for making libraries of all expressed genes in biopsies taken from one patient with intestinal type of metaplasia, without dysplasia and from normal squamous epithelium. For validation of results normal squamous and BE biopsies of 20 patients was used. Results: Over 45,000 tags were sequenced and analysed for each library. Statistical analysis revealed that 776 tags were significantly differentially expressed ($p<0.05$) comparing squamous esophagus and BE. From these tags, 72 were more than 10-fold up-regulated and 26 were more than 10-fold down-regulated in BE. Genes were clustered in different functional classes and mapped on the genome. The most up-regulated tags in BE were Trefoil factor (TFF) 1, TFF2, TFF3, Annexin A10, Fatty Acid Binding Protein-1 and Galectin 4. The SAGE libraries showed significantly increased levels of Cytokeratin (CK's) 7, 8, 18, 19 and 20 in BE, while the CK's 4, 5, 6A, 6B and 13 were significantly less expressed in BE when compared to squamous epithelium. The specific CK patterns were validated by immunohistochemistry. Conclusions: This study provides us with a comparison of the transcriptomes of BE and squamous epithelium and gives us important insight in pathways and genes that are involved in the development of BE.

Expression profiles of coeliac disease biopsies during mucosa recovery*

B Diosdado[1], H van Bakel[1], MC Wapenaar[1], L Franke[1], JWR Meijer[2], ML Mearin[3], CJJ Mulder[4], C Wijmenga[1]. [1]Complex Genetics Section, DBG-Department of Medical Genetics, University Medical Centre, Utrecht; [2]Department of Pathology, Rijnstate Hospital, Arnhem; [3]Department of Paediatrics, Paediatrician Unit of Paediatric Gastroenterology, Leiden University Medical Centre, Leiden;[4] Department of Gastroenterology, VUmc, Amsterdam; the Netherlands.

Coeliac disease (CD) is a multifactorial, gluten-sensitive enteropathy of unknown pathogenesis that comprises in three stages of development: Marsh I (lymphocytosis), Marsh II (lymphocytosis and crypt hyperplasia), and Marsh III (lymphocytosis and crypt hyperplasia and villous atrophy). Treatment with a gluten-free diet (GFD) normalizes the mucosa of the small intestine of these patients.
To define the molecular pathways of CD pathogenesis and the tissue remodeling mechanisms upon treatment with a GFD, we analyzed the expression profiles of 48 CD biopsies taken at different stages of the disease following a GFD and 21 controls.
The samples were hybridized in duplo on microarray slides containing >21,000 genes. Data analysis was performed by MANOVA and Gene Spring software.
The analysis revealed 158 differentially expressed genes involved in the tissue recovery of CD. The genes could be divided into two groups based on their pattern of expression. The first group comprises 102 genes that show a gradual up-regulated pattern of expression towards mucosa normalization. These genes are implicated in enterocyte differentiation processes and represent the functionality of the duodenum. The second group of genes consists of 56 genes that are mainly related to immuno-logical pathways. Many of these genes are regulated by interferon-γ and their pattern of expression shows a gradual down-regulation of the immune response after gluten withdrawal.
Interestingly, our data do not show changes in expression of genes of previously proposed mechanisms in CD, such as apoptosis, oxidative stress or metalloproteinases pathways.
Our results reveal that during the mucosa recovery in CD, there are two opposite processes taking place. There is a gradual release of the immune response and a complementarily up-regulation of genes re-stabilising the normal homeostasis of the mucosa of the small intestine.

Expression profiling of the recovering mucosa in coeliac disease reveals the molecular basis of the pleiotropic clinical features

Martin C. Wapenaar[1], Begoña Diosdado[1], Jos W.R. Meijer[2], Chris J.J. Mulder[3], and Cisca Wijmenga[1].

[1]DBG-Department of Medical Genetics, University Medical Center Utrecht, Utrecht; [2]Department of Pathology, Rijnstate Hospital, Arnhem; and [3]Department of Gastroenterology, VU Medical Center, Amsterdam, The Netherlands.

The gluten-induced inflammatory response in coeliac disease (CD) yields a flattened small intestinal mucosa. Loss of villi is accompanied by clinical symptoms that vary from common features like diarrhea, fatigue, and failure to thrive, to more specific complications like anemia, osteoporosis, infertility, nutrient malabsorption, and vitamin deficiency. The basic question is whether these impairments are solely the consequence of absorptive surface reduction due to villous atrophy. Untreated patients (UT) put on a gluten-free diet (T) sequentially recover from villous atrophy, crypt hyperplasia, and lymphocytosis through stages referred to as Marsh III, II, I, and 0 (normalized). We have determined the expression profile of 21,000 genes, using oligonucleotide microarrays, in duodenal biopsy samples from 69 individuals (48 patients and 21 normal controls). By using patients in various stages of remission, we established the expression profile of all these genes as a function of the recovery sequence: MIII-UT (12), MIII-T (7), MII (10), MI (8), and M0 (11). Here we focus on all the genes upregulated during remission that showed a profile of gradual increase, correlating for ≥ 95% with that of the classical brush border enzyme dipeptidyl peptidase IV. This yielded a list of 594 genes involved in various processes like the uptake, transport, metabolism, and modification of sugars (33), lipids (37) and proteins (29), mostly confined to the brush border membrane. Additionally, genes involved in detoxification (23), cholesterol and steroid processing (20), vitamin (A, C, D, K) metabolism, iron transport, anion (calcium, potassium, sodium) and water flux. The diverse clinical features of CD may be accounted for by the reduced activity of the aforementioned genes. The general picture that emerges from this expression analysis is that CD is mainly an epithelial disorder where the terminal differentiation of enterocytes is impaired due to the gluten-induced immune response.

MET signalling in primary colon epithelial cells leads to increased transformation irrespective of aberrant Wnt signalling

E.M.J. Boon[1], M. Kovarikova[2], P. Derksen[1], R. van der Neut[1]. Dept of Pathology[1] Academic Medical Center, Amsterdam, The Netherlands, Institute of Biophysics[2], Acad. Sci. Czech Rep., Brno, Czech Republic

It has been shown that in hereditary and most sporadic colon tumours components of the Wnt pathway are mutated. The Wnt target MET has been implicated in the development of colon cancer. Here, we show that overexpression of wild type or a constitutively activated form of MET in colon epithelial cells leads to increased transformation irrespective of Wnt signalling. Fetal human colon epithelial cells without aberrant Wnt signalling were transfected with wild type or mutated MET constructs. Expression of these constructs leads to increased phosphorylation of MET and its downstream targets PKB and MAPK. Upon stimulation with HGF, the expression of E-cadherin is downregulated in wild type MET transfected cells, whereas cells expressing mutated MET show low E-cadherin levels independent of stimulation with ligand. This implies a higher migratory propensity of these cells. Furthermore, fetal human colon epithelial cells expressing the mutated form of MET have colony forming capacity in soft agar, while cells expressing wild type MET show an intermediate phenotype. Subcutaneous injection of mutated MET transfected cells in nude mice leads to the formation of tumours within 12 days in all mice injected. At this time point mock-transfected cells do not form tumours while wild type MET transfected cells form subcutaneous tumours in 1 out of 5 mice. We thus show that MET signalling can lead to increased transformation of colon epithelial cells independent of Wnt signalling and in this way could play an essential role in the onset and progression of colorectal cancer.

TRAIL induces apoptosis in human colorectal adenomas and human colorectal adenoma cell lines

M. Jalving[1,2], J.J. Koornstra[1,2], S. de Jong[2], N. Zwart[3], W. Boersma-van Ek[1], J. Wesseling[3], E.G.E. de Vries[1], J.H. Kleibeuker[2]. Dept of Gastro-enterology[2], University Medical Center Groningen, The Netherlands.

Non-steroidal anti-inflammatory drugs (NSAIDs) reduce the risk of colorectal cancer. However, the chemopreventive effect of NSAIDs is incomplete and associated with significant side effects indicating the need for other chemopreventive drugs. Recombinant human (rh) TNF-related apoptosis-inducing ligand (TRAIL) has strong anticancer properties in vitro and in animal studies without affecting normal colon epithelium. Colorectal adenomas, like carcinomas, show increased expression of the pro-apoptotic TRAIL receptors DR4 and DR5 compared to normal tissue, suggesting potential sensitivity to TRAIL induced apoptosis. The aim of this study was to investigate whether adenomas are sensitive to TRAIL induced apoptosis.Two human adenoma cell lines (VACO-235 and VACO-330) were studied and short-term ex vivo cultures of human adenoma tissue sections (n=28) were established. From each adenoma two sections were cultured for 5 hours, one of which in the presence of rhTRAIL. Apoptosis in adenoma derived cell lines was determined by immunocytochemistry, fluorimetric caspase assays and western blotting. Apoptosis in the short-term cultures was determined by light microscopy using morphological criteria. rhTRAIL treatment of adenoma cell lines resulted in induction of apoptosis and was associated with caspase-3 and caspase-8 activation and PARP cleavage. The sensitivity of adenoma cells to rhTRAIL was comparable with colon cancer cell lines. In the short-term cultures, more apoptosis was observed in TRAIL treated adenoma tissue segments compared with their control counterparts (apoptotic index 28 ± 19 % vs 18 ± 11 %, p=0.008). Apoptosis induction was stronger in adenomas with high-grade dysplasia than those with low-grade dysplasia.Colorectal adenoma cells are sensitive to rhTRAIL-induced apoptosis. The ability of TRAIL to induce apoptosis in adenoma cells suggests the potential application of this drug in colorectal cancer chemoprevention.

The specificity of CDX-2 and cytokeratin expression as biomarkers in Barrett's esophagus

J.W.P.M. van Baal[1], F. Milano[1], A.M. Rygiel[1], A. Bozikas[1], J.J.G.H.M. Bergman[2], S.J.H. van Deventer[1], M.P. Peppelenbosch[3], K.K. Krishnadath[3], Dept. of Experimental Internal Medicine, AMC, Amsterdam[1], Dept of Gastroenterology and Hepatology, AMC, Amsterdam[2], Dept of Cell Biology, Rijks Universiteit Groningen, Groningen[4], The Netherlands

Background: Barrett's esophagus (BE) is a premalignant condition in which normal squamous epithelium of the lower esophagus is replaced by columnar epithelium containing intestinal metaplasia. For diagnostic purposes it is important to find biomarkers that can specifically identify BE, for instance to differentiate short segments of Barrett epithelium from stomach cardia. Several bio-markers, including certain cytokeratins (CKs) are specifically expressed in BE. Recently CDX-2, a homeobox gene, involved in intestinal mucosal cell proliferation and differentiation, has been suggested to be highly expressed in BE. AIM: To determine the specificity of CDX-2 and a set of CKs (7, 8, 18 and 20) as specific markers for BE as compared to normal squamous esophageal and cardia tissue. Immunohistochemistry with specific antibodies against CDX-2, CK 7, 8, 18 and 20 was performed on fresh frozen consecutive tissue sections of normal squamous (S), cardia (C) and non dysplastic Barrett's epithelium of 20 patients. RT-PCR for these markers was used to determine expression on RNA level. Results: Immunohistochemically, CDX-2 was found to be expressed in the nucleus of 73% of all Barrett tissues. This homeobox gene was not expressed in gastric cardia or normal squamous tissue. CK 7, 8, 18 and 20 were expressed in all Barrett biopsies and negative in normal squamous epithelium. CK 8, 18 and 20 were expressed in cardia. CK 7 showed positive expression in 27% of cardia biopsies. RT-PCR showed high expression of CK 7, 8, 18 and 20 in Barrett tissue. These CKs were negative in squamous tissue; CK 8, 18 and 20 were found positive in cardia tissue, while CK 7 was expressed at a very low level.
Conclusion: CK 7, 8, 18, 20 and CDX-2 can be used as biomarkers to distinguish between Barrett and normal squamous cells. In order to distinguish Barrett from cardia tissue, a combination of CDX-2 and CK 7 is most informative.

Alfabetische lijst van standhouders voorjaarscongres 2005

Altana Pharma BV	B 24
Alvleesklliervereniging	K 9
AstraZeneca	B 31
Aventis Pharma BV	K 17
Bipharma Diagnostics BV	B 22
Boston Scientific Benelux BV	K 15
Cobra Medical BV	K 7
Cook Nederland BV	B 8
Crohn en Colitis Ulcerosa Ver. Nederland	K 14
Danica Nederland BV	K 18
Elan Pharma BV	K 20
Endomed BV	B 6
Endosoft BV	B 1a
Endotechniek	K 3
Erbe Nederland BV	B 29
Eurosteriel Medical BV	K 19
Ferring BV	B 28
FMH Medical BV	B 1
Fresenius Kabi Nederland BV	K 16
Hitachi Medical Systems	B 19
Janssen Cilag BV	K 23
Lans Medical BV	B 2
Maag Lever Darm Stichting	K 10
Medical Measurements Systems BV	B 25
Medicor	B 11
Medtronic BV Gastro-Uro	B 4
Merck Sharp & Dohme BV	B 13
Meridian Bioscience	K 21
Minntech-Medivators	B 10
Nederlandse Coeliakie Vereniging	K 11
Norgine BV	B 21
Novartis Pharma	K 2a
Nutricia Nederland BV	B 26
Nycomed Nederland BV	K 4
Opleidingsinstituut Erasmus MC	K 8
Paes Nederland BV	B 20
Pentax Medical	B 5
Pfizer BV	B 7
Roche Nederland BV	K 2
S. Schrijver bemiddeling voor gepensioneerde specialisten	K 5
Sanofi-Synthelabo	B 30
Schering-Plough BV	K 22
Sigma-tau Ethifarma BV	B 23
Solvay Pharma BV	B 14
Stichting Opsporing Erfelijke Tumoren	K 6
Stichting Specifieke Scholing Verpleegkundigen	K 13
Stöpler Instrumenten & Apparaten BV	B 12
Tramedico	K 1
Tyco Healthcare Nederland BV	B 15
UCB Pharma BV	B 27
Uniprom Diagnostics	B 16
Van Straten Medical	K24a
Vandeputte Medical	B 17
Vereniging Ziekte van Hirschsprung	K 12
Wassenburg & Co BV	B 9
Winclove Bio Industries BV	B 3
Yakult Nederland BV	B 18
Zambon Nederland BV	K 24

B = Beneluxhal K = Kempenhal

Plattegrond expositie

AANMELDINGSFORMULIER VOOR HET LIDMAATSCHAP VAN DE NEDERLANDSE VERENIGING VOOR GASTROENTEROLOGIE

Naam : M/V*
Voorletters :
Geboortedatum :
Titel :
Specialisme :
Assistent in opleiding voor :

Werkadres
instituut :
afdeling :
straat :
postcode en plaats :
telefoon :
e-mail :

Huisadres
straat :
postcode en plaats :
telefoon :

Doctoraalexamen : ja/neen*; zo ja, welke studierichting:
Datum artsexamen : d.d. . . . . ./n.v.t.*
Inschrijving MSRC : ja/neen*, zo ja, welk:
Speciale interesses op GE-gebied :

geeft zich hierbij graag op als : lid/buitengewoon lid* van de NVGE
(contributie € 35,- per jaar)

Tevens wil ondergetekende zich aansluiten bij:
o Sectie Gastrointestinale Endoscopie
o Netherlands Society of Parenteral and Enteral Nutrition
o Sectie Neurogastroenterologie en Motiliteit
o Sectie Experimentele Gastroenterologie
o Sectie Kindergastroenterologie
o Nederlandse Vereniging voor Gastrointestinale Chirurgie
contributie (m.i.v. 1-1-2005)
- o Specialisten € 90,00 (totaal € 125,00 incl. lidmaatschap NVGE € 35,00)
- o Assistenten i.o. € 25,00 (totaal € 60,00 incl. lidmaatschap NVGE € 35,00)

(graag aankruisen wat voor u van toepassing is)

Toezending verenigingspost aan huis-/werkadres*.

Datum: Handtekening:

_____

Sturen aan de secretaris van de NVGE:
Postbus 657, 2003 RR Haarlem

* doorhalen wat niet van toepassing is.

U kunt zich tevens aanmelden via de website van de NVGE: www.nvge.nl
N.B. Het lidmaatschap loopt per kalenderjaar. Opzeggen dient vóór 1 december te gebeuren.

AANMELDINGSFORMULIER VOOR HET LIDMAATSCHAP VAN DE NEDERLANDSE VERENIGING VOOR HEPATOLOGIE

Naam	:	M/V*
Voorletters	:	
Geboortedatum	:	
Titel	:	
Specialisme	:	
Assistent in opleiding voor	:	

Werkadres

instituut	:
afdeling	:
straat	:
postcode en plaats	:
telefoon	:
e-mail	:

Huisadres

straat	:
postcode en plaats	:
telefoon	:

Doctoraalexamen	: ja/neen*; zo ja, welke studierichting:
Datum artsexamen	: d.d. . . . . ./n.v.t.*
Inschrijving MSRC	: ja/neen*, zo ja, welk:
Speciale interesses op hepatologisch gebied	:

geeft zich hierbij graag op als : lid/buitengewoon lid*
contributie: € 25,00 per jaar

Toezending verenigingspost aan huis-/werkadres*.

Datum: Handtekening:

_____

Sturen aan de secretaris van de NVH:
Postbus 657
2003 RR Haarlem

*doorhalen wat niet van toepassing is

N.B. Het lidmaatschap loopt per kalenderjaar. Opzeggen dient vóór 1 december te gebeuren.

Nederlandse vereniging voor Gastro-Enterologie

SEVA Sectie endoscopie verpleegkundigen en assistenten

AANMELDINGSFORMULIER LIDMAATSCHAP NVGE / SEVA

Naam : M / V*
Evt. meisjesachternaam :
Voorletters :
Geboortedatum :

Werkadres
Instituut :
Afdeling :
Straat :
Postcode en plaats :
Telefoon :
e-mail :

Huisadres
Straat :
Postcode en plaats :
Telefoon :

geeft zich hierbij op als lid van de Sectie Endoscopie Verpleegkundigen en Assistenten van de NVGE tot schriftelijke wederopzegging. *Let wel, het lidmaatschap is persoonsgebonden en niet overdraagbaar. Verenigingspost zal uitsluitend naar uw huisadres worden gestuurd.*

U bent verpleegkundige / doktersassistent(e) anders nl,……*

Datum:…… Handtekening:…….

** aangeven wat van toepassing is.*

☐ Hierbij machtig ik de penningmeester van de Sectie Endoscopie Verpleegkundigen en Assistenten om de verschuldigde contributie, ad. € 15 per jaar, tot wederopzegging automatisch van mijn bankrekening af te laten schrijven. Betaling geschiedt pas nadat u door de eerstvolgende ledenvergadering als lid bent aangenomen.

Indien u geen machtiging tot incasso geeft ontvangt u automatisch een acceptgiro.

Bankrekeningnummer Handtekening

☐☐☐☐☐☐☐☐☐ …….

N.B. Het lidmaatschap loopt per kalenderjaar. Opzeggen dient dus vóór 1 januari te gebeuren.

Dit formulier sturen naar:
Centraal Secretariaat NVGE (ledenadministratie SEVA)
Postbus 657 - 2003 RR Haarlem

AANMELDINGSFORMULIER
LIDMAATSCHAP NVGE/VMDLV

Naam : M / V*
Evt. meisjesachternaam :
Voorletters :
Geboortedatum :

Werkadres
Instituut :
Afdeling :
Straat :
Postcode en plaats :
Telefoon :
E-mail :

Huisadres
Straat :
Postcode en plaats :
Telefoon :

BIG registratienummer : _____ datum registratie:_____

geeft zich hierbij op als lid van de Vereniging Maag Darm Lever Verpleegkundigen van de Nederlandse Vereniging voor Gastroenterologie tot schriftelijke wederopzegging. *Let wel, het lidmaatschap is persoonsgebonden en niet overdraagbaar. Verenigingspost zal uitsluitend naar uw huisadres worden gestuurd.*

Datum:…… Handtekening:…….

** aangeven wat van toepassing is.*

☐ Hierbij machtig ik de penningmeester van de Vereniging Maag Darm Lever Verpleegkundigen om de verschuldigde contributie, ad. € 27,50 per jaar, tot wederopzegging automatisch van mijn bank-/girorekening af te laten schrijven. Betaling geschiedt pas nadat u door de eerstvolgende ledenvergadering als lid bent aangenomen.

Indien u geen machtiging tot incasso geeft ontvangt u automatisch een acceptgiro.

(Post)bankrekeningnummer Handtekening

…….

N.B. Het lidmaatschap loopt per kalenderjaar. Opzeggen dient volgens de statuten vier weken voor het aflopen van het kalenderjaar **schriftelijk** te gebeuren.

Dit formulier sturen naar:
Centraal Secretariaat NVGE (ledenadministratie VMDLV)
Postbus 657
2003 RR Haarlem