Programma najaarsvergadering 5 en 6 oktober 2006

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 diverse ledenvergaderingen:

Assistentenvereniging Touché (mdl-artsen i.o.)	5 oktober, 12.15 uur - Zaal 82/83
Nederlandse Vereniging voor Gastroenterologie	5 oktober, 21.30 uur - Brabantzaal

INHOUDSOPGAVE pag.

VRIJDAG 6 OKTOBER 2006

Ochtendprogramma

Middagprogramma

Tijdstippen diverse ledenvergaderingen:

Nederlandse Vereniging voor Hepatologie	6 oktober, 08.30 uur - Parkzaal
Sectie Endoscopie Verpleegkundigen en Assistenten	6 oktober, 11.30 uur - Diezezaal
Sectie Experimentele Gastroenterologie	6 oktober, 11.45 uur - Parkzaal
Nederlands Genootschap van Maag-Darm-Leverartsen	6 oktober, 12.00 uur - Zaal 80-82

VOORWOORD

Hierbij treft u het volledige programma aan van de najaarsvergadering die gehouden wordt op 5 en 6 oktober a.s. in Congrescentrum Koningshof te Veldhoven.

Het programma zal donderdag 5 oktober om 11.00 uur van start gaan met een symposium van de Nederlandse Vereniging voor Hepatologie: 'Nuclear Receptors in Hepatology 2006'. Alle overige sessies beginnen na de lunch om 13.30 uur. Op donderdagmiddag is er de Minibattle van de Nederlandse Vereniging voor Gastrointestinale Chirurgie (thema's slokdarm en rectum) en een Symposium 'Viscerale pijn' van de Sectie Neurogastroenterologie en Motiliteit. Daarnaast uiteraard enkele sessies met vrije voordachten: van de NVGIC en de NVH.
Aan het eind van de middag wacht u tijdens een plenaire sessie de uitreiking van de Astra-Zeneca Gastrointestinale Research Award 2006 in de Brabantzaal. De winnaar van deze prestigieuze prijs zal in aansluiting aan de uitreiking een erevoordracht houden.

De plenaire donderdagavondsessie biedt de Presidential Selection en aansluitend de Altana Lecture, die dit keer verzorgd wordt door Prof. dr. C. Hawkey uit Notttingham. Alle aanwezigen worden van harte uitgenodigd bij deze sessie aanwezig te zijn!

Op vrijdag zijn er in de ochtend twee symposia, over Infectie preventie en Intestinal Failure. Daarnaast vragen wij uw speciale aandacht voor de Frieda den Hartog Jager Lecture die verzorgd wordt door Prof. dr. J.J.B. van Lanschot, om 11.30 uur in de Baroniezaal.
Verder zijn er deze dag sessies met vrije voordrachten van Nederlandse Vereniging van Gastroenterologie, de Sectie Gastrointestinale Endoscopie en de Sectie Experimentele Gastroenterologie. De laatste sectie organiseert v.a. 11.00 uur in de Parkzaal tevens de 'International Teaching Session' die deze maal verzorgd wordt door Prof. dr. J.C. Clevers van het Hubrecht Laboratorium in Utrecht. In respectievelijk de Diezezaal en het Auditorium worden tot slot door de Sectie Endoscopie Assistenten en Verpleegkundigen en de Vereniging Maag Darm Lever Verpleegkundigen eigen programma's met lezingen verzorgd.

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 dit programma zijn ingezonden door leden van de Sectie Kindergastroenterologie.*

Belangrijke mededeling
over de aanwezigheid van farmaceutische industrieën

Aan alle deelnemers aan de najaarsvergadering

De Nederlandse Vereniging voor Gastroenterologie kent een jarenlange samenwerking met de farmaceutische industrie. De vereniging stelt de farmaceutische industrie in de gelegenheid aanwezig te zijn bij de wetenschappelijke vergaderingen met een stand. Mede hierdoor kan de vereniging haar wetenschappelijke bijeenkomsten organiseren.
In het "besluit van 31 oktober 1994, Stb. 787, houdende regels voor reclame voor geneesmiddelen (Reclamebesluit Geneesmiddelen)" is onder andere geregeld wat wel en wat niet is toegestaan ten aanzien van gunstbetoning voor artsen door de farmaceutische industrie.
De wet zegt dat - onder strikte voorwaarden - de farmaceutische industrie alleen reclame mag maken voor receptgeneesmiddelen voor personen die bevoegd zijn om dergelijke geneesmiddelen voor te schrijven. Alle andere personen (inclusief bijvoorbeeld verpleegkundigen, endoscopie assistenten en biochemici) worden beschouwd als "publiek". De farmaceutische industrie mag geen reclame maken voor receptgeneesmiddelen voor publiek.
De Nederlandse Vereniging voor Gastroenterologie is een wetenschappelijke vereniging voor personen die beroepsmatig betrokken zijn bij zorg, onderwijs en onderzoek ten behoeve van patiënten met maag-, darm- en leveraandoeningen. Dat betekent dat ook personen die geen arts zijn, lid van de NVGE kunnen zijn.
De aanwezigheid van artsen, niet-artsen en farmaceutische industrieën tijdens de voorjaarsvergadering kan de NVGE ongewild in aanraking brengen met de inspectie voor de gezondheidszorg, sectie reclametoezicht en daarmee in diskrediet worden gebracht.
Dat willen wij te allen tijde voorkomen.

Wij delen u dan ook het volgende mede:
Reclame-uitingen en merkproductinformatie van farmaceutische industrieën in het voorliggende programmaboekje zijn alleen gericht op personen die bevoegd zijn om de betreffende geneesmiddelen voor te schrijven.
Al het aanwezige reclamemateriaal, reclame-uitingen en merkproductinformatie van farmaceutische industrieën die aanwezig zijn op het voorjaarscongres, zijn alleen bedoeld en alleen gericht op personen die bevoegd zijn om de betreffende geneesmiddelen voor te schrijven.
Wij maken u erop attent dat het voor niet-artsen dan ook niet is toegestaan de stands van de aanwezige farmaceutische industrieën te bezoeken.

De NVGE en farmaceutische industrie (sponsoren) meent u allen, en met name de niet BIG geregistreerde personen, voldoende te hebben ingelicht en kunnen niet verantwoordelijk worden gehouden indien u geen acht slaat op deze mededeling.

Het bestuur van de NVGE

Woensdag 4 oktober 2006

Voorzitter:	**Prof. dr. C.J.J. Mulder**
20.00 – 20.20	Ursodeoxycholzuur, werkingsmechanismen en klinische relevantie *Prof. dr. R.J.P Oude Elferink, MDL, Academisch Medisch Centrum*
20.30 – 20.50	Genetisch bepaalde cholestatische syndromen *Dr. R.H.J. Houwen, kindergeneeskunde-MDL, UMC Utrecht*
21.00 – 21.20	Alcoholisch leverlijden, behandelbaar? *Prof. dr. P.L.M. Jansen, MDL, Academisch Medisch Centrum*
21.30 – 21.50	Auto-immuun hepatitis en overlapbeelden. *Dr. H.R. van Buuren, MDL, Erasmus MC*

Donderdag 5 oktober 2006

Voorzitter:	**Dr. R.A. de Man**
08.00 – 08.20	Pathogenese en behandeling van NASH *Dr. G.H. Koek, MDL, Academisch Ziekenhuis Maastricht*
08.30 – 08.50	Acute HCV infectie: afwachten of behandelen? *Dr. R.A. de Man, MDL, Erasmus MC*
09.00 – 09.20	Behandeling van chronische HCV infectie *Dr. R.J. de Knegt, MDL, Erasmus MC*
09.30 – 09.50	Behandeling van chronische HBV infectie *Prof. dr. H.L.A. Janssen, MDL, Erasmus MC*
	Koffiepauze
10.30 – 10.50	Hepatorenaal syndroom en SBP *Drs. M.J. Coenraad, MDL, Leids Universitair Medisch Centrum*
11.00 – 11.20	Hepatopulmonaal syndroom/pulmonale hypertensie en de lever *Dr. H.J. Bogaard, Academisch Medisch Centrum*
11.30 – 11.50	Indicatie en Selectie voor Levertransplantatie *Dr. E.B. Haagsma, MDL, Universitair Medisch Centrum Groningen*
12.00 – 12.30	Levertransplantatie: wat is er opgelost en waar moeten we nog een antwoord op vinden? *Prof. dr. M.J.H. Slooff, Heelkunde, Universitair Medisch Centrum Groningen*

Programma donderdag 5 oktober 2006

DONDERDAG	BRABANTZAAL	BARONIEZAAL	PARKZAAL	AUDITORIUM	DIEZEZAAL
13.00	Vrije voordrachten Nederlandse Vereniging voor Gastrointestinale Chirurgie p. 10	Symposium 'Viscerale Pijn' p. 14	Start NVH **symposium 'Nuclear Receptors in Hepatology 2006'** om **10.30** uur. Vrije voordrachten Nederlandse Vereniging voor Hepatologie v.a. 13.00 uur p. 10	Geen programma in deze zaal op de donderdag	Geen programma in deze zaal op de donderdag
15.00	Theepauze	Theepauze	Thee / ledenvergadering		
15.30	**Minibattle 'Endoscopische versus operatieve behandeling van slokdarm- en rectumtumoren'** p. 13	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie p. 15	Vrije voordrachten Nederlandse Vereniging voor Hepatologie p. 17		
17.00	**Uitreiking AZ Award 2006**				
17.30	Congresborrel expositiehal	Congresborrel expositiehal	Vervolg symposium tot 17.30		
18.00	Diner in Genderzaal	Diner in Genderzaal	Diner Genderzaal		Diner in de Genderzaal
20.00	Presidential Selection en **Altana Lecture C.J. Hawkey** p. 21				
21.30	**Ledenvergadering NVGE**				
22.30	Congresborrel Brabantzaal				

Programma vrijdag 6 oktober 2006

VRIJDAG	BRABANTZAAL	BARONIEZAAL	PARKZAAL	AUDITORIUM	DIEZEZAAL
08.30	Casuïstiek voor de clinicus om *9.00 uur gevolgd door* Vrije voordrachten Sectie Gastrointestinale Endoscopie p. 22	**Symposium:** **'Intestinal Failure'** p. 23	Vrije voordrachten Nederlandse Vereniging voor Hepatologie (klinisch) p. 25		
10.00	Koffiepauze	Koffiepauze om 09.40	Koffiepauze	Ontvangst en koffie VMDLV	Ontvangst en koffie SEVA
10.30	**Symposium** **'Infectie Preventie'** p. 22	**Vervolg Symposium** **'Intestinal Failure'** 11.30 uur: **Frieda den Hartog Jager Lecture** door Prof. dr. J.J.B. van Lanschot p. 25	Vrije voordrachten Sectie Experimentele Gastroenterologie gevolgd door (om 11.00 uur): **International Teaching Session** p. 27-28	Programma Vereniging Maag Darm Lever Verpleegkundigen p. 35	Programma Sectie Endoscopie Verpleeg-kundigen en Assistenten p. 34
12.00	Lunch in expositiehal	Lunch in expositiehal	Lunch in expositiehal		12.30 Lunch in expositiehal
13.30	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie p. 28	Vrije voordrachten Nederlandse Vereniging voor Gastrointestinale Chirurgie en NESPEN p. 29	Vervolg vrije voordrachten Sectie Experimentele Gastroenterologie p. 31	Programma Vereniging Maag Darm Lever Verpleegkundigen p. 35	Vervolg programma Sectie Endoscopie Verpleeg-kundigen en Assistenten p. 34
15.00	Thee / einde programma	Thee / einde programma	Thee / einde programma		Einde programma

Donderdag 5 oktober 2006

Nederlandse Vereniging voor Hepatologie **Parkzaal**

10.00 Inschrijving, koffie

Symposium: 'Nuclear Receptors in Hepatology 2006'

10.30 NR in fatty liver disease
Prof. dr. Michael Muller, Wageningen

11.00 NR in cholestasis
Prof. dr. Saul Karpen, Houston, U.S.A.

11.30 NR in gallstone disease
Dr. Antonio Moschetta, Bari, Italy

12.00 Lunch

Nederlandse Vereniging voor Gastrointestinale Chirurgie **Brabantzaal**

12.30 Inschrijving, koffie

Voorzitters: M.H.A. Bemelmans en B.F. Huizinga

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

13.00 Relation between 18FDG-PET standardised uptake values and prognosis in oesophageal cancer patients (p.36)
J.M.T. Omloo[1], M. Westerterp[1], R. Boellaard[2], O.S. Hoekstra[2], G.W. Sloof[3], J.J.B. van Lanschot[1]. Depts of Surgery[1] and Nuclear Medicine[3], Academic Medical Centre, University of Amsterdam and Dept of Nuclear Medicine and PET research[2], Free University Medical Centre, Amsterdam, The Netherlands

13.10 Patient preference for information on prognosis after potentially curative esophagectomy (p. 37)
S.M. Lagarde[1], ,J.R. van Werven[1], S.J. Franssen[2], E.M.A. Smets[2], H.C.J.M. de Haes[2], J.J.B. van Lanschot[1]. Depts of Surgery[1] and Medical Psychology[2], Academic Medical Center at the University of Amsterdam, The Netherlands

13.20 Role of (18)-FDG-PET-scan in preoperative management of oesophageal carcinoma (p. 38)
C.A.S. Berende[1], C. Hoekstra[2], R.A.M.J. Claessens[2], K. Bosscha[1]. Depts of Surgery[1] and nuclear medicine[2], Jeroen Bosch Hospital, 's Hertogenbosch, The Netherlands

13.30 Liver Resection for Non Colorectal Metastasis (p. 39)
J. Kist[1], A.J.C. IJtsma[1], C.S. van der Hilst[2], A.S.H. Gouw[3], P.M.J.G. Peeters[1], R.J. Porte[1], K.P. de Jong[1], M.J.H. Slooff[1]. Dept of Hepatopancreatobiliary Surgery and Liver Transplantation[1] and depts of Medical Technology Assessment[2] and of Pathology[3], University Medical Centre Groningen, Groningen, The Netherlands

13.40 Clinical utility of COX-2 promoter hypermethylation in gastric cancer (p. 40)
M.F.G. de Maat[1,2], C.J.H. van de Velde[1], N. Umetani[2], P. de Heer[1], P.J.K. Kuppen[1], A.J. Bilchik[3], R.A.E.M. Tollenaar[1] and D.S.B. Hoon[2]
Dept of Surgery[1], Leiden University Medical Center, Leiden, The Netherlands, Dept of Molecular Oncology[2] and div of Gastrointestinal Surgery[3], John Wayne Cancer Institute, Santa Monica, CA, U.S.A.

13.50 Outcome after liver resection in the elderly (p. 41)
L.M.S. Boevé[1], A.J.C. IJtsma[1], C.S. van der Hilst[2], P.M.J.G. Peeters[1], R.J. Porte[1], K.P. de Jong[1], M.J.H. Slooff[1]. Dept of Hepatopancreatobiliary, Surgery and Liver Transplantation[1], Dept of Medical Technology Assessment[2], University Medical Centre Groningen, Groningen, The Netherlands

14.00 Incidence and management of chyle leakage after pancreatoduodenectomy (p. 42)
N.A. van der Gaag[1], A.C. Verhaar[1], O.R.C. Busch[1], T.M. van Gulik[1], D.J. Gouma[1] , Dept of Surgery, Amsterdam Medical Centre, Amsterdam, The Netherlands

Donderdag 5 oktober 2006

14.10 Effectiveness and morbidity of 68 needle catheter jejunostomies installed after major abdominal surgery (p. 43)
C.A.S. Berende, M.F. Ernst, W.A.H. Gelderman, K. Bosscha. Dept of Surgery, Jeroen Bosch Hospital, 's Hertogenbosch, the Netherlands

14.20 Malpractice Litigation by Bile Duct Injury patients: associated factors for submitting a claim and the effect of the verdict on Quality of Life (p. 44)
P.R. de Reuver[1], M.A. Sprangers[2], D.J. Gouma[1]. Dept of Surgery[1] and Medical Psychology[2], Amsterdam Medical Centre, Amsterdam, The Netherlands

14.30 Acute appendicitis: a meta-analysis of test accuracy related to prevalence of disease (p. 45)
A. van Randen[1,2], S. Bipat[2], J. Stoker[2], M.A. Boermeester[1]. Depts of Surgery[1], and Radiology[2], Academic Medical Center Amsterdam, The Netherlands

14.40 Emergency surgery for perforated diverticulitis: outcome after Hartmann's procedure or primary anastomosis of 217 cases (p. 46)
J. Vermeulen[1], G.P. Akkersdijk[2], G.H. Mannaerts[3], E. van der Harst[1], P.P.L.O. Coene[1], W.F. Weidema[2], J.F. Lange[4]. Dept of surgery Medical Center Rijmond-zuid[1], Ikazia Hospital[2], Sint Franciscus Hospital[3], Erasmus Medical Center[4], Rotterdam, The Netherlands

14.50 A systematic review on the significance of extracapsular lymph node involvement in gastrointestinal malignancies (p. 47)
J. Wind[1], S.M. Lagarde[1], F.J.W. ten Kate[2], W.A. Bemelman[1], J.J.B. van Lanschot[1]. Depts of Surgery[1] and Pathology[2], Academic Medical Center Amsterdam, The Netherlands

15.00 Theepauze

Voorzitters: R. van Hillegersberg en C.J.H.M. van Laarhoven

Minibattle **'Endoscopische versus operatieve behandeling van slokdarm- en rectumtumoren'**

Slokdarm

15.30 Endoscopische behandeling van het vroege oesophagus carcinoom. Wie heeft nog behoefte aan een chirurg?
Dr. J.J.G.H.M. Bergmann, maag-darm-leverarts, AMC, Amsterdam

15.42 Operatieve behandeling van het vroege oesophagus carcinoom.
Prof. dr. H Tilanus, chirurg, Erasmus MC Rotterdam.

15.54 Discussie

Rectum

16.09 Endomucosale behandeling van het villeuze adenoom van het rectum:
Dr. H.M. van Dullemen, maag-darm-leverarts, UMC Groningen

16.21 Minimaal invasieve behandeling middels TEM procedure van het villeuze adenoom van het rectum
Dr. E. de Graaf, chirurg, IJsselland ziekenhuis, Capelle aan de IJssel

16.33 Operatieve behandeling van het villeuze adenoom van het rectum:
Dr. G. Beets, chirurg, Academisch Ziekenhuis Maastricht

16.45 Discussie

17.00 Sluiting Minibattle

Donderdag 5 oktober 2006

Nederlandse Vereniging voor Gastroenterologie **Brabantzaal**

Voorzitter: J.B.M.J. Jansen

17.00 Uitreiking van de **AstraZeneca Gastrointestinale Research Award 2006** door de voorzitter van de jury, gevolgd door een erevoordracht door de prijswinnaar

17.30 Congresborrel

18.00 Diner in de Genderzaal

20.00 Vervolg programma in de Brabantzaal

Sectie Neurogastroenterologie en Motiliteit **Baroniezaal**

Voorzitter: M.A. Benninga

Symposium 'Viscerale pijn'

13.00 Pathophysiologie
Prof. dr. G.E.E. Boeckxstaens, AMC, Amsterdam

13.25 Abdominal bloating
Prof. F. Azpiroz, Hospital General Vall d'Hebron, Barcelona, Spain

13.55 Klinische benadering van viscerale pijn
Prof. dr. M. Samsom, UMC Utrecht

14.25 Hypnotherapie
Dr. V. Miller, University of Manchester, UK

15.00 Einde programma

Voordrachten inclusief discussie

Nederlandse Vereniging voor Gastroenterologie **Baroniezaal**

Voorzitters: P.D. Siersema en C.M.F. Kneepkens

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

15.00 Immunoglobulin-free light chains mediate the activation of mouse dorsal root ganglion neurons by antigens (p. 48)
A. Rijnierse[1], A.B.A. Kroese[2,3], F.A.M Redegeld[1], M.W. van der Heijden[1], B.R.J. Blokhuis[1], A.S. Koster[1], J-P. Timmermans[3], F.P. Nijkamp[1], A.D. Kraneveld[1] [1]Division of Pharmacology & Pathophysiology, Utrecht Institute of Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands, [2]Institute for Risk Assessment Sciences, University of Utrecht and Department of Surgery, University Medical Centre Utrecht, the Netherlands, [3]Laboratory of Cell Biology and Histology, Department of Biomedical Sciences, University of Antwerp, Antwerp, Belgium

15.10 Do drugs with anticholinergic properties increase the risk of reflux esophagitis? A study in a large Dutch GP database (p. 49)
E.M. van Soest[1,2], J.D. Dieleman[2], P.D. Siersema[1], L. Schoof[2], M.C.J.M. Sturkenboom[2,3], E.J. Kuipers[1]. Dept of Gastroenterology and Hepatology[1], and Medical Informatics[2], and Epidemiology and Biostatistics[3], Erasmus MC, Rotterdam, The Netherlands

15.20 The effect of oral administration of ursodeoxycholic acid and proton pump inhibitors in patients with Barrett's esophagus (p. 50)
J.J. Bergman[1], A. Bozikas[1,2], W.A. Marsman[1], W.D. Rosmolen[1], J.W. van Baal[2], W. Kulik[4], F.J. ten Kate[3], K.K. Krishnadath[1]. Depts of Gastroenterology and Hepatology[1], Experimental Internal Medicine[2], Pathology[3], Genetic Metabolic Diseases[4], Academic Medical Center, Amsterdam, The Netherlands

15.30 The most optimal strategy to detect distant metastases in patients with esophageal cancer (p. 51)
E.P.M. van Vliet[1], E.W. Steyerberg[2], M.J.C. Eijkemans[2], E.J. Kuipers[1], P.D. Siersema[1]. Depts of Gastroenterology and Hepatology[1] and Public Health[2], Erasmus MC - University Medical Center Rotterdam, The Netherlands

Donderdag 5 oktober 2006

15.40 Test first or treat first? A randomized comparison of treatment strategies for dyspepsia (p. 52)
M.J.R. Janssen[1], R.J.F. Laheij[1], W.A. de Boer[1,2] and J.B.M.J. Jansen[1]. Dept of Gastroenterology and Hepatology[1], Radboud University Nijmegen Medical Centre, Nijmegen, Bernhoven Hospital[2], Oss, The Netherlands

15.50 High prevalence of intraepithelial lymphocytosis (Marsh I and II) in duodenal biopsies in a large cohort of patients referred for routine gastro-duodenoscopy (p. 53)
I.M. Harkema[1], J.J. Kolkman[1], J.J. van Baarlen[2]. Depts of Gastro-enterology[1] and Pathology[2], Medical Spectrum Twente Hospital, Enschede, The Netherlands

16.00 Post-absorptive plasma citrulline levels fail to discriminate healthy controls from patients with malabsorption due to severe villous atrophy (p. 54)
J.H.C. Peters[1], N.J. Wierdsma[2], M.A.E. van Bokhorst - de van der Schueren[2], C.J.J Mulder[1] and A.A. van Bodegraven[1]. Dept of Gastro-enterology, small bowel unit[1], and Dept of Nutrition and Dietetics[2], VU medical centre, Amsterdam, The Netherlands

16.10 Cholestatic bile salt concentrations do not affect proliferation or differrentiation of intestinal epithelial cells in vitro* (p. 55)
E.L. Los, H. Wolters, A. Baghdasaryan, F. Kuipers, H.J. Verkade, E.H.H.M. Rings. Dept of Pediatrics, University Medical Center Groningen, University of Groningen, The Netherlands

16.20 Folate and colon cancer (p. 56)
Final Report Maag Lever Darm Stichting projectno. WS 99-72
J. Keijer[1], L. Pellis[1,2], M. van der Donk[2] and E. Kampman[2]. RIKILT-Institute of Food Safety[1], Wageningen University[2], Wageningen, The Netherlands

16.30 Prevalence of abdominal symptoms in recreational runners competing in a long-distance run: an observational study in 1281 subjects (p. 57)
R.W.F. ter Steege, J.J. Kolkman. Dept of Gastroenterology, Medical Spectrum Twente, Enschede, The Netherlands

16.40 Atherosclerotic risk factors in patients with chronic splanchnic syndrome (p. 58)
R.P. Veenstra[1], R.H. Geelkerken[1], A.B. Huisman[1], P.B.F. Mensink[2], C. Doelman[1] and J.J. Kolkman[1]. Medical Spectrum Twente Enschede[1] Erasmus Medical Center[2] Rotterdam, The Netherlands

16.50 Haemorrhoid Artery Ligation (HAL) for second to fourth degree haemorrhoids - a pilot study (p. 59)
M.E Witte, J.M Klaase. Dept of Surgery, Medical Spectrum Twente, Enschede, The Netherlands

17.00 Voor de uitreiking van de **AstraZeneca Gastrointestinale Research Award 2006** kunt u zich begeven naar de Brabantzaal

Nederlandse Vereniging voor Hepatologie (basaal) — Parkzaal

Voorzitter: K.N. Faber en L. van der Laan

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

13.00 A transcription-based copper sensor enables analysis of copper homeostasis in living cells (p. 60)
P.V.E van den Berghe[1], H.E.M. Malingré[1], B. van de Sluis[1], R. Berger[1], W. Schaffner[3], M. Merkx[4], C. Wijmenga[2], L.W.J. Klomp[1]. Depts of Metabolic and Endocrine Diseases[1] and of Complex Genetics[2], University Medical Center Utrecht, The Netherlands, Institut für Molekularbiologie[3], Universität Zürich, Germany. Dept of Protein Engineering[4], Technical University Eindhoven, The Netherlands

13.15 Peroxisome proliferator-activated receptor α (PPARα) is an important determinant of hepatic carbamoylphosphate synthetase I (CPS I) expression, both in vitro and in vivo. (p. 61)
I.C. Gaemers, J.M. Stallen and W.H. Lamers. Academic Medical Center, Liver Center, Amsterdam, The Netherlands

13.30 COMMD proteins as a novel family of regulators of copper homeostasis (p. 62)
P. de Bie[1,2], B. van de Sluis[1,2], W.I.M. Vonk[1,2], E. Burstein[3], R. Berger[1], C. Wijmenga[2], L.W.J. Klomp[1]. Laby of Metabolic and Endocrine Diseases[1], Complex Genetics Section, DBG-Department of Medical Genetics[2], University Medical Center, Utrecht, The Netherlands, Dept of Internal Medicine[3], University of Michigan Medical School, Ann Arbor, USA

Donderdag 5 oktober 2006

13.45 Increased activity of hypoxia-inducible factor 1 leads to early embryonic lethality in Commd1 null mice. (p. 63) *B. van de Sluis[1,2], P. Muller[2], L.W. Klomp[2], K. Duran[1], T. van Harn[2], A. Chen[3], P.P. Liu[4], C. Wijmenga[1]. Complex Genetics Section, DBG Dept of Medical Genetics[1] and Lab for Metabolic and Endocrine Diseases[2], University Medical Center Utrecht, The Netherlands, Genetic Disease Research Branch[3] and Oncogenesis and Development Section[4], NHGRI, National Institutes of Health, Bethesda, MD 20*

14.00 A Specific Intestinal Cholesterol Secretion Pathway Contributes to Cholesterol Removal (p. 64) *C.L.J. Vrins[1], A.E. v.d. Velde[1], K. v.d. Oever[1], C. Kunne[1], P.C.N. Rensen[2], A.K. Groen[3]. AMC Liver Center[1] and dept of Medical Biochemistry[3], AMC, Amsterdam and Dept Endocrinology and Metabolism[2], Leiden University Medical Center, Leiden, The Netherlands*

14.15 Enhanced biliary cholesterol secretion in Atp8b1 mutant mice is Abcg5/8 in-dependent. (p. 65) *A. Groen, C. Kunne, G. Jongsma, K. van den Oever, K.S. Ho-Mok, C.C. Paulusma, R.P.J. Oude Elferink. AMC Liver Center, Academic Medical Center, Amsterdam, The Netherlands*

14.30 ABCB11 activity is regulated by the cholesterol content of the canalicular membrane. (p. 66) *R.P.J. Oude Elferink, A. Groen, K.S. Ho-Mok, C. Kunne, L.N. Bull[2], C.C. Paulusma. AMC Liver Center[1], Academic Medical Center, Amsterdam, The Netherlands, UCSF Liver Center and Dept of Medicine[2], San Francisco General Hospital, Univ. of California San Francisco, USA*

14.45 Interaction of ATP8B1 with CDC50A/B is required for endoplasmic reticulum exit and plasma membrane flippase activity. (p. 67)
C.C. Paulusma, K.S. Ho-Mok and R.P.J. Oude Elferink. AMC Liver Center, Academic Medical Center, Amsterdam, The Netherlands

15.00 Theepauze

Voorzitters: H.L.A. Janssen en C.C. Paulusma

15.30 Functional donor dendritic cells migrate after liver transplantation via the bloodstream into the recipient (p. 68) *B.M. Bosma[1], H.J. Metselaar[1], J.G. Kusters[1], T.C.K. Tran[2], H.W. Tilanus[2], E.J. Kuipers[1], J. Kwekkeboom[1]. Erasmus MC- University Medical Center, Dept. of Gastroenterology and Hepatology[1] and Surgery[2] Rotterdam, the Netherlands*

15.45 TNF-α partially abrogates regulatory T cell mediated suppression of the anti-HBV immune response in patients with a chronic infection. (p. 69)
J.N. Stoop, P.J. Biesta, J.G. Kusters, E.J. Kuipers, H.L.A. Janssen, R.G. van der Molen. Dept of Gastroenterology and Hepatology, Erasmus MC-University Hospital Rotterdam, The Netherlands

16.00 Increased risk of hepatocellular carcinoma among patients with hepatitis C cirrhosis and diabetes mellitus (p. 70)
B.J. Veldt[1], W. Chen[2], E..J. Heathcote[2], H. Wedemeyer[3], J. Reichen[4], W.P. Hofmann[5], S. Zeuzem[5], M.P. Manns[3], B.E. Hansen[1,6], H.L.A. Janssen[1]. Depts of Gastroenterology & Hepatology[1] and Epidemiology & Biostatistics[6], Erasmus MC University Medical Center, Rotterdam, The Netherlands, Toronto Western Hospital, University Health Network[2], Toronto, Canada, Dept of Gastroenterology, Hepatology and Endocrinology[3], Medizinische Hochschule Hannover, Germany. Institute of Clinical Pharmacology[4], University of Berne, Berne, Switzerland, Universitätsklinikum des Saarlandes[5], Klinik fur Innere Medizin II, Homburg/Saar, Germany

16.10 Mycophenolic Acid Inhibits Hepatitis C Virus Replication Independent Of Guanosine Depletion And Acts In Synergy With Interferon-α (p. 71)
S.D. Henry[1], H.J. Metselaar[2], A. Kok[1], B.L. Haagmans[3], H.W. Tilanus[1] and L.J.W. van der Laan[1]. Depts of Surgery[1], Gastroenterology & Hepatology[2] and Virology[3], Erasmus MC-University Medical Center, Rotterdam, The Netherlands

16.20 Randomized placebo controlled phase I/II trial of a-galactosylceramide (KRN7000) for the treatment of chronic hepatitis C (p. 72)
B.J. Veldt[1], H.J.J. van der Vliet[2]*, B.M.E. von Blomberg[3], H. van Vlierberghe[4], G. Gerken[5], N. Nishi[6], K. Hayashi[6], R.J. Scheper[3], R.J. de Knegt[1], A.J.M. van den Eertwegh[7], H.L.A. Janssen[1], C.M.J. van Nieuwkerk[8]. Dept of Gastroenterology & Hepatology[1], Erasmus MC University Medical Center Rotterdam, The Netherlands, Depts of Internal Medicine[2], Pathology[3], Oncology[7] and Gastroenterology and Hepatology[8], Free University Medical Center, Amsterdam, The Netherlands. Dept of Gastroenterology and Hepatology[4], Ghent University Hospital, Ghent, Belgium, Klinik für Gastroenterologie und Hepatologie[5], Universitätsklinikum Essen, Essen, Germany. Pharmaceutical division[6], Kirin Brewery Co. Ltd., Tokyo, Japan*

Donderdag 5 oktober 2006

16.30 Nasobiliary drainage induces complete and long-lasting remission in benign recurrent intrahepatic cholestasis* (p. 73)
J.M. Stapelbroek[1] K.J. van Erpecum[2], L.W.J. Klomp[3], N.G. Venneman[2], M.P. Schwartz[2], C.M.J. van Nieuwkerk[4], A.S. Knisely[5], R.H.J. Houwen[1]. Depts of Pediatric Gastroenterology[1] and Gastroenterology[2], Lab for Metabolic and Endocrine Diseases[3], University Medical Center Utrecht, The Netherlands; Dept of Gastroenterology[4], VU Medical Center Amsterdam, The Netherlands, Institute of Liver Studies[5], King's College Hospital, London, UK

16.40 ALT flares occur often after delivery in patients with chronic hepatitis B virus infection (p. 74)
M.J. ter Borg, W.F. Leemans, R.A. de Man, H.L.A. Janssen. Dept of Gastroenterology and Hepatology, Erasmus MC, University Medical Center Rotterdam, The Netherlands

16.50 Efficacy and prediction of response in a single center cohort of chronic hepatitis B patients treated with adefovir dipivoxil (p. 75)
W.F. Leemans[1], B.E. Hansen[2], H.G.M. Niesters[3], H.L.A. Janssen[1], R.A. de Man[1]. Depts of Gastroenterology & Hepatology[1], Epidemiology and Biostatistics[2], and Virology[3], Erasmus MC, University Medical Center, Rotterdam, The Netherlands

17.00 The impact of intraoperative findings on the surgical treatment strategy of patients with colorectal liver metastases (p. 76)
M.R. van den Bergh[1], M.R. Meijerink[2], S. Meijer[1], M.P. van den Tol[1]. Dept of Surgery, and Surgical Oncology[1] and dept of Radiology[2], VU Medical Center, Amsterdam, The Netherlands

17.10 Einde programma, congresborrel

18.00 Diner in Genderhal

Presidential Selection (plenaire sessie) **Brabantzaal**

Voorzitter: J.B.M.J. Jansen

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

20.00 The progression of premalignant gastric lesions to gastric cancer in the Netherlands (p. 77 + 78)
A.C. de Vries[1], N.C.T. van Grieken[2], M.K. Casparie[3], G.A. Meijer[2], E.J. Kuipers[1]. Dept of Gastroenterology and Hepatology[1], Erasmus MC University Medical Center, Rotterdam, Dept of Pathology[2], VU Medical Center, Amsterdam, The Netherlands PALGA (Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief), the nationwide network and registry of histo- and cytopathology[3], The Netherlands

20.15 Validation of the O-POSSUM-score in patients with oesophageal cancer (p. 79)
A.K.D. Maris, S.M. Lagarde, S.M.M. de Castro, O.R.C. Busch, H. Obertop, J.J.B van Lanschot.. Dept of Surgery, Academic Medical Center at the University of Amsterdam, The Netherlands

20.30 Metformin protects hepatocytes against oxidative stress induced apoptosis via HO-1 induction and inhibition of JNK activation (p. 80)
L. Conde de la Rosa[1], T.E. Vrenken[1], M. Buist-Homan[1], P. L. Jansen[2], H. Moshage[1]. Depts Gastroenterology and Hepatology, University Medical Center Groningen[1] and Academic Medical Center Amsterdam[2], The Netherlands

20.45 Gastrojejunostomy versus stent placement in patients with malignant gastric outlet obstruction: a comparison in 95 patients (p. 81)
S.M. Jeurnink[1], E.W. Steyerberg[2], G. van 't Hof[1], C.H.J. van Eijck[3], E.J. Kuipers[1], P.D. Siersema[1]. Departments of Gastroenterology and Hepatology[1], Public Health[2] and Surgery[3], Erasmus MC Rotterdam, The Netherlands

21.00 **Altana lecture**
NSAID's in relation to gastrointestinal disease
Prof. dr. C.J. Hawkey, University Hospital Nottingham U.K.

21.30 Ledenvergadering Nederlandse Vereniging voor Gastroenterologie

Vrijdag 6 oktober 2006

Casuïstiek **Brabantzaal**

Voorzitter: W. Hameeteman

08.30 Casuïstische patiëntenbespreking

Sectie Gastrointestinale Endoscopie **Brabantzaal**

Voorzitter: W. Hameeteman

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

09.0 The GI Mentor II simulator: validation and learning curves (p. 82 + 83)
A.D. Koch[1], S.N. Buzink[3], J. Heemskerk[2], S.M.B. Botden[2], R.H.M. Goossens[3], H. de Ridder[3], R. Veenendaal[4], J.J. Jakimowicz[2], E.J. Schoon[1]. Depts of Gastroenterology[1] and Surgery[2], Catharina Hospital Eindhoven, Faculty of Industrial Design Engineering[3], Delft University of Technology[4], University Medical Center Leiden, The Netherlands

09.10 Stents are safe and effective for the palliation of malignant strictures near the upper esophageal sphincter (p. 84)
E.M.L. Verschuur, E.J. Kuipers, J. Haringsma, P.D. Siersema. Dept of Gastroenterology & Hepatology, Erasmus MC/University Medical Center Rotterdam, The Netherlands

09.20 Video autofluorescence imaging for dysplasia and cancer detection in patients with longstanding ulcerative colitis (p. 85)
F.J.C. van den Broek, M. Kara, J.C. Hardwick, P.C. Stokkers, P. Fockens, E. Dekker. Dept of Gastroenterology and Hepatology, Academic Medical Center Amsterdam, The Netherlands

09.30 Inter-observer agreement amongst non-expert endoscopists of narrow band imaging of early neoplasia in Barrett's esophagus (p. 86)
W. Curvers[1], R. Lindeboom[1], L. Baak[2], C. Bohmer[3], R. Mallant-Hent[4], A. van Oijen[5], C. Ponsioen[6], P. Scholten[7], K. Krishnadath[1], P. Fockens[1], J. Bergman[1]. Academic Medical Center[1], Onze Lieve Vrouwe Gasthuis[2], St Lucas Andreas Hospital[7], Amsterdam; Spaarne Hospital[3], Hoofddorp, Flevo Hospital[4], Almere, Medical Center Alkmaar[5], Hospital Hilversum[6], The Netherlands

09.40 Sporadic duodenal adenoma and colorectal neoplasia (p. 87)
D. Ramsoekh[1], M.E. van Leerdam[1], R.J.Th. Ouwendijk[2], E.J. Kuipers[1]. Depts of Gastroenterology and Hepatology, Erasmus Medical Center[1], Rotterdam and Ikazia Hospital[2], Rotterdam, The Netherlands

09.50 How effective is the disinfection of endoscopes? (p. 88)
A.J. Buss[1], M.H. Been[1], R.P. Borgers[2], I. Stokroos[3], H.C. van der Mei[4], W. Melchers[5], A.J. Limburg[2], J.E. Degener[1]. Depts of Medical Microbiology[1], Endoscopy Center[2], Cell Biology[3] and of BioMedical Engineering[4], University Medical Center Groningen, Dept of Medical Microbiology[5], University Medical Center Nijmegen, The Netherlands

10.00 Koffiepauze

Symposium Infectiepreventie **Brabantzaal**

Voorzitter: W. Hameeteman

Voorlopig programma (10.30 – 12.00 uur)

Desinfectie in de endoscopie
Prof. dr. J.F.W.M. Bartelsman, mdl-arts
Afdeling Maag-Darm-Leverziekten, Academisch Medisch Centrum Amsterdam

Endocarditis preventie
Prof. dr. J. van der Meer, internist
Afdeling Infectieziekten, Academisch Medisch Centrum Amsterdam

Symposium in het kader van het emeritaat van Prof. dr. P.B. Soeters (AZM)

Voorzitters: Prof. dr. P.B. Soeters en Dr. C.H.C. Dejong

08.30	Opening door C.H.C. Dejong (voorzitter NESPEN)
08.40	Short bowel syndrome bij volwassenen in Nederland, een databank! *Dr. G. Dijkstra (UMCG)*
09.00	Thuis parenterale voeding bij volwassenen en kinderen. *Prof. dr. H.P. Sauerwein (AMC)*
09.20	Enterocutane fisteling: *Dr. W.G. van Gemert (azM)*
09.40	Koffiepauze
10.00	Short bowel syndrome bij kinderen in Nederland *inventarisatie van 15 jaar behandeling.* *Mw. Dr. J.C. Escher (Erasmus MC, Rotterdam)*
10.20	Intestinal failure: de peri-medische zorg *Mw. C.F. Jonkers (AMC)*
10.50	Treatment of intestinal failure. Current status and future directions *Prof. G. Carlson, Hope Intestinal Failure Centre, U.K.*
11.20	Afsluiting door Prof. dr. P.B. Soeters
11.30	Einde symposium

Nederlandse Vereniging voor Gastroenterologie — Baroniezaal

Voorzitter: J.B.M.J. Jansen

11.30 **Frieda den Hartog Jager Lecture**
Nieuwe ontwikkelingen in de diagnostiek en behandeling van patiënten met een oesophagus carcinoom?
Prof. dr. J.J.B. van Lanschot, chirurg, AMC, Amsterdam

Nederlandse Vereniging voor Hepatologie (klinisch) — Parkzaal

08.30 Ledenvergadering Nederlandse Vereniging voor Hepatologie

Voorzitters: R.H.J. Houwen en H.W. Reesink

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

09.00 Assessment of tumor growth in relation with increase of future remnant liver volume and function in patients undergoing preoperative portal vein embolization (p. 89)
W. de Graaf[1], K. P. van Lienden[2], R. Makay[1], A.K.van Vliet[1], R.J. Bennink[3], T. M. van Gulik[1]. Depts of Surgery / Surgical Laboratory[1], Radiology[2], and Nuclear Medicine[3], Academic Medical Center, University of Amsterdam, The Netherlands

09.10 Health Related Quality of Life of hepatitis C patients in the DITTO-study (p. 90)
G. Bezemer[1], E. Verheij-Hart[1], R.J. de Knegt[1], B. Hansen[1], S. Zeuzem[2], J.M. Pawlotsky[3], A.U. Neumann[4], G. Germanidis[5], R. Pakula[6], C. Ferrari[7], J.I. Esteban[8], M. Lagging[9], F. Negro[10], S.W. Schalm[1], for the DITTO-HCV Study Group. Erasmus MC University Hospital of Rotterdam[1], The Netherlands, Saarland University Hospital[2], Homburg/Saar, Germany, Hopital Henri Mondor - Universite Paris XII[3], Creteil, France; Bar-Ilan University[4], Ramat-Gan, Israel; Aristotle University of Thessaloniki[5], Thessaloniki, Greece; Tel Aviv Sourasky Medical Center[6], Tel-Aviv, Israel; Azienda Ospedaliera di Parma[7], Parma, Italy; Hospital General Vall d'Hebron[8], Barcelona, Spain, University of Göteborg[9], Göteborg, Sweden; Hospital University of Geneve[10], Geneve, Switzerland

Vrijdag 6 oktober 2006

09.20 Double-dose peginterferon-α2b induction plus ribavirin in chronic hepatitis C patients with previous nonresponse to interferon monotherapy or combination therapy with ribavirin (p. 91)
J.F. Bergmann[1], J.M. Vrolijk[1], P. van der Schaar[2], K.J. van Erpecum[3], B. van Hoek[4], A. van der Sluys Veer[5], R. de Vries[6], B.E. Hansen[7], H.L.A. Janssen[1], S.W. Schalm[1], R.J. de Knegt[1]. Depts of Gastroenterology & Hepatology, Erasmus Medical Center[1], Rotterdam, Atrium Medical Center[2], Heerlen, University Medical Center Utrecht[3], Leiden University Medical Center[4], Onze Lieve Vrouwe Gasthuis[5], Amsterdam, Hospital Rijnstate[6], Arnhem, Dept. Epidemiology and Biostatistics[7], Erasmus University Rotterdam, The Netherlands.

09.30 Modeling of pharmacokinetics and viral kinetics in HBeAg-positive chronic hepatitis B treated with pegylated interferon alpha-2b (p. 92)
M.J.ter Borg[1], B.E. Hansen[1,2], E. Herrmann[4,5], S. Zeuzem[4], B.L. Haagmans[3], H.L.A. Janssen[1]. Depts of Gastroenterology & Hepatology[1], Epidemiology & Biostatistics[2], and Virology[3], Erasmus MC, University Medical Centre Rotterdam, The Netherlands, Saarland University[4], Faculty of Medicine and Darmstadt University of Technology[5], Faculty of Mathematics, Germany

09.40 Early peginterferon alpha-2b induced HBeAg loss results in increased rates of HBsAg loss and undetectable HBV DNA (p. 93)
E.H.C.J. Buster[1], M. van Zonneveld[1], B.E. Hansen[1,2], E. Verheij[1], H.L.A. Janssen[1]. Depts of Gastroenterology and Hepatology[1], and Epidemiology and Biostatistics[2], Erasmus MC University Medical Center Rotterdam, Rotterdam, The Netherlands

09.50 Peginterferon alpha-2b is well tolerated and leads to high virological and histological response rates in chronic hepatitis B patients with advanced fibrosis (p. 94)
E.H.C.J. Buster[1], M. van Zonneveld[1], P.E. Zondervan[2], B.E. Hansen[1,3], E. Verheij[1], S.W. Schalm[1], H.L.A. Janssen[1]. Depts of Gastroenterology and Hepatology[1], Pathology[2], and Epidemiology and Biostatistics[3], Erasmus MC University Medical Center Rotterdam, The Netherlands

10.00 Koffiepauze

Sectie Experimentele Gastroenterologie **Parkzaal**

Voorzitters: J.G. Kusters en E.H.H.M. Rings

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

10.30 Expression of lipo-oligosaccharide ganglioside mimics protects Campylobacter jejuni from phagocytosis by human THP-1 monocytes (p. 95)
M.P. Bergman[1], R. Abdilahi Ibrahim[1], P. Crocker[2], A.P. Heikema[1], H.P. Endtz[1] and A. van Belkum[1]. Dept of Medical Microbiology and Infectious Diseases[1], Erasmus MC, Rotterdam, The Netherlands; Welcome Trust Biocentre, School of Life Sciences[2], University of Dundee, Dundee, UK.

10.40 The TNF-β polymorphism NcoI is associated with an increased risk of developing Barrett's esophagus and esophageal adenocarcinoma in gastro-esophageal reflux disease (p. 96)
V. Menke, J.G. Kusters, R.G.J. Pot, L.M.G. Moons, P.D. Siersema, E.J. Kuipers. Dept of Gastroenterology and Hepatology, Erasmus MC - University of Rotterdam, Rotterdam, The Netherlands

10.50 Matrix metalloproteinase-9 mediated VEGF release contributes to neoangiogenesis in colon cancer (p. 97)
K. Zuidwijk, L.J.A.C. Hawinkels, H.W. Verspaget, E.S.M. de Jonge-Muller, R.D. Fontein[1], V. Ferreira[1], I. Biemond, C.F.M. Sier. Dept of Gastroenterology-Hepatology, University Medical Center Leiden, Dept of Biochemistry, Academic Medical Center, Amsterdam[1], The Netherlands

Sectie Experimentele Gastroenterologie **Parkzaal**

11.00 **International Teaching Session**
'Wnt, stem cells and cancer of the intestine'
Prof. dr. J.C. Clevers, Hubrecht Laboratorium, Utrecht

11.45 Ledenvergadering Sectie Experimentele Gastroenterologie

12.15 Lunchbuffet expositiehal

Nederlandse Vereniging voor Gastroenterologie **Brabantzaal**

Voorzitter: R.J.F. Felt-Bersma en A.J.P. van Tilburg

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

13.30 Dose-dependent influence of 5-ASA on thiopurine metabolism (p. 98)
N.K.H. de Boer[1], D. Wong[2], P.M. Hooymans[2], B. Jharap[1], P. de Graaf[3], C.J.J. Mulder[1], L.G.J.B. Engels[4] and A.A. van Bodegraven[1]. Depts of Gastroenterology and Hepatology, VU Medical Center,Amsterdam[1] and Maasland Hospital in Sittard[4], Clinical Pharmacy, Maasland Hospital, Sittard[2] and VU University Medical Center, Amsterdam[3], The Netherlands

13.40 Surveillance for colorectal carcinoma in patients with inflammatory bowel disease: are AGA and BSG guidelines adequate? (p. 99)
M.W.M.D. Lutgens, F.P. Vleggaar, B. Oldenburg, M. Samsom. Dept of Gastroenterology, University Medical Center Utrecht, The Netherlands

13.50 A Panel of genes in pediatric-onset inflammatory bowel disease compared with healthy controls and adult-onset inflammatory bowel disease* (p. 100)
L. de Ridder[1], R.K. Weersma[2], G. Dijkstra[2], G. van der Steege[2], M.A. Benninga[1], I.M. Nolte[2], J.A.J.M. Taminiau[1], D.W. Hommes[3], P.C.F. Stokkers[3]. Emma Childrens Hospital/Academic Medical Center[1] and University Medical Center[2], Groningen, Academic Medical Center[3], Amsterdam, The Netherlands

14.00 Bi-allelic MUTYH mutations are found in a significant number of Dutch MUTYH-associated polyposis coli (MAP) patients, but not in patients with between 1-10 polyps or HNPCC. (p. 101)
(MLDS voordracht MWO 03-55)
M. Nielsen[1], P.F. Franken[2], M.M. Weiss[1], H.J. van Kranen[3], J.Th. Wijnen[1], H. Morreau[4], M.H. Breuning[1], C.M.J. Tops[1], R. Fodde[2], H.F.A. Vasen[5,6], F.J. Hes[1]. Center of Human and Clinical Genetics[1], Leiden University Medical Center, Dept of Pathology[2], Josephine Nefkens Institute, Erasmus University Medical Center[3] The National Institute for Public Health and the Environment (RIVM); Dept of Pathology[4], Leiden University Medical Center, Foundation for the Detection of Hereditary Tumors[5], Leiden, The Netherlands

14.20 Increased risk of colorectal neoplasia in asymptomatic liver transplant recipients. (p. 102)
J.J. Koornstra[1], J. Wesseling[2], A.E. de Jong[3], H.F.A. Vasen[3], J.H. Kleibeuker[1], E.B. Haagsma[1]. University Medical Center Groningen, Depts of Gastroenterology & Hepatology[1] and Pathology[2], Foundation for the detection of Hereditary Tumors[3], Leiden, The Netherlands

14.30 Genetic Aspects of Chronic Pancreatitis. (p. 103)
Final report Maag Lever Darm Stichting projectno. WS 00-21
M. Verlaan, J.P.H. Drenth, J.B.M.J. Jansen. Dept of Gastroenterology and Hepatology, St Radboud University Medical Center, Nijmegen, The Netherlands.

14.40 Polyp multiplicity and colorectal cancer. Over 10^7 simulations to meet scientific standards ? (p. 104)
K.W. Geul[1], J.D.F. Habbema[1], C.W. Ting[1], J.H.P. Wilson[1], F.T. Bosman[2], E.J. Kuipers[1], Erasmus Medical Center Rotterdam[1], The Netherlands, Institut Universitaire de Pathologie[2], Lausanne University, Switzerland

14.50 Neoplasia of the rectal stump in patients with inflammatory bowel disease. (p. 105)
S. Meijvis[1], R. van Hogezand[2], J. van der Woude[3], D. de Jong[4] and B. Oldenburg[1] on behalf of the Initiative on Crohn and Colitis (ICC). University Medical Center Utrecht[1], Leiden University Medical Center[2], Erasmus Medical Center Rotterdam[3], St Radboud Medical Centre Nijmegen[4], The Netherlands.

15.00 Theepauze

Ned. Vereniging voor Gastrointestinale Chirurgie en NESPEN — Baroniezaal

Voorzitters: C.H.C. Dejong en R.J. Porte

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

13.30 The introduction of laparoscopic colorectal surgery in daily practice (p. 106)
A.G.J. Aalbers and G.H.H. Mannaerts. Dept of Surgery, St Franciscus Gasthuis, Rotterdam, The Netherlands

Vrijdag 6 oktober 2006

13.40 Ex-vivo sentinel lymph node mapping in patients with colorectal cancer (p. 107)
P.M. van Schaik[1], J.C. van der Linden[2], M.F. Ernst[1], W.A.H. Gelderman[1], K. Bosscha[1]. Depts of Surgery[1] and Pathology[2] Jeroen Bosch Ziekenhuis, Den Bosch, The Netherlands

13.50 Dysplasia in the ileal pouch after restorative proctocolectomy for ulcerative colitis: A systematic review (p. 108)
P.J. van Koperen[1], M. Scarpa[3], D.W. Hommes [2], W.A. Bemelman[1]. Dept of Surgery, Academic Medical Center, University of Amsterdam, The Netherlands, Dept of Gastroenterology[2], Leiden University Medical Center, The Netherlands, Dept of Surgical and Gastroenterological Sciences[3], University of Padova, Italy

14.00 Detection of colorectal cancer using MALDI-TOF serum protein profiling (p. 109)
M.E. de Noo[1], A.M. Deelder[2], M.P.J. van der Werff [2], R.A.E.M. Tollenaar[1]. Depts of Surgery[1] and Parasitology[2], Leiden University Medical Center, The Netherlands

14.10 Nutritional management for acute pancreatitis: adherence to guidelines in a large cohort of patients in the Netherlands (p. 110)
B.M.W. Spanier[1], J. de Graaf[1], M.G.W. Dijkgraaf[2], M.J. Bruno[1]. Depts of Gastroenterology and Hepatology[1] and Clinical Epidemiology and Biostatistics[2], Academic Medical Center, Amsterdam, The Netherlands

14.20 High-fat enteral feeding after hemorrhagic shock preserves gut wall integrity (p. 111)
J. de Haan, T. Lubbers, M. Hadfoune, M.D. Luyer, W.A. Buurman, J.W. Greve. Dept of Surgery, Nutrition and Toxicology Institute Maastricht, Maastricht University, University Hospital Maastricht, The Netherlands

14.30 The effect of anti-oxidant enriched nutrition on oxidative stress after major upper gastro-intestinal tract surgery; a randomized clinical trial (p. 112)
G.C. Melis[1], P.G. Boelens[1], P.G. Scheffer[2], J. Diks[1], A.R.J. Girbes[3], M.A. Cuesta[1], T. Teerlink[2], J.W.R. Twisk[4], P.A.M. van Leeuwen[1]. Depts of Surgery[1], Clinical Chemistry[2], Intensive Care[3], Epidemiology and Biostatistics[4], VU medical center, Amsterdam, The Netherlands

14.40 Carbohydrate digestion and absorption in a rat model of cholestasis* (p.113) *E.L. Los, H. Wolters, R. Havinga, T. Boer, K. Bijsterveld, F. Stellaard, F. Kuipers, H.J. Verkade, E.H.H.M. Rings. Dept of Pediatrics, University Medical Center Groningen, University of Groningen, The Netherlands*

14.50 Gastric emptying of two carbohydrate-rich beverages, observed with scintigraphy (p. 114) *G.C. Melis[1], M. Richir[1], M. Garretsen[1], H.J. Pijpers[2], P.A.M. van Leeuwen[1]. Depts of Surgery[1] and Nucleair Medicine[2], VU Medical Center, The Netherlands*

15.00 Einde programma, theepauze

Sectie Experimentele Gastroenterologie — Parkzaal

Voorzitter: G. Dijkstra en E.A.F. van Tol

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

13.30 Defective Pathogen Recognition and Anti-Apoptotic Pathways in Dendritic Cells from NOD2 Mutant Crohn`s Disease Patients (p.115)
Z. Zelinkova[1], A.J. van Beelen[3], F. de Kort[1], P.D. Moerland[4], P.E. Verloren van Themaat[4], A.A. te Velde[1], S.J. van Deventer[1], E.C. de Jong[3], D.W. Hommes, Dept of Gastroenterology and Hepatology[1], Laboratory of Experimental Internal Medicine[2], Dept of Cell Biology & Histology[3], Bioinformatics Laboratory[4], Dept of Clinical Epidemiology, Biostatistics and Bio-informatics, Academic Medical Center, Amsterdam, The Netherlands

13.40 Urease-induced calcium precipitation by bile-resistant Helicobacter species may initiate gallstone formation (p. 116). *C. Belzer, J.G. Kusters, E.J. Kuipers, A.H.M. van Vliet. Dept of Gastroenterology and Hepatology Erasmus MC-University Medical Center, Rotterdam, The Netherlands.*

13.50 A high fat diet down-regulates gene expression of cholesterol efflux transporters in the small intestine of mice (p.117)
H.M. van den Bosch[1,2], N.J. de Wit[1,2], H. Vermeulen[1,2], G.J. Hooiveld[1,2], F. Kuipers[2], M. Müller[1,2], R. van der Meer[1,2]. Dept of Human Nutrition[1], Wageningen University, Wageningen Center for Food Sciences[2], The Netherlands

Vrijdag 6 oktober 2006

14.00 Altered intestinal motility in mice orally sensitized with cow's milk proteins (p. 118)

B. Schouten[1], E.C.A.M. van Esch[1], G.A. Hofman[1], L.E.M. Willemsen[1], J. Garssen[1,2]. Div of Pharmacology and Pathophysiology[1], University of Utrecht, Dept of Immunology[2], Numico Research B.V. Wageningen, The Netherlands

14.10 Expression of matrilysin in gastrointestinal neoplasia infers a dualistic function (p. 119)

L.J.A.C. Hawinkels, H.W. Verspaget, K. Zuidwijk, M. van den Berg, E.S.M. de Jonge-Muller, R. Hanemaaijer[1], V. Ferreira[2], C.F.M. Sier. Dept of Gastroenterology-Hepatology, Leiden University Medical Center, TNO Quality of Life Biomedical Research[1], Leiden, Dept of Biochemistry[2], Academic Medical Center, Amsterdam, The Netherlands

14.20 Prevalence of a second urease gene cluster in Helicobacter species colonising the carnivore stomach (p. 120)

J. Stoof[1], R.G.J. Pot[1], D. van der Neut[1], S.C. Schuster[2], E.J. Kuipers[1], J.G. Kusters[1], A.H.M. van Vliet[1]. Dept of Gastroenterology and Hepatology, Rotterdam Erasmus MC-University Medical Center, Rotterdam, The Netherlands[1], Pennsylvania State University, Center for Comparative Genomics and Bioinformatics[2], University Park, PA, USA

14.30 How Barrett's esophagus (BE) develops: the role of chronic inflammation in BE induction (p. 121)

V. Menke, J.G. Kusters, R.W.F. de Bruin, R.R. Sital, H. van Dekken, E.J. Kuipers, P.D. Siersema. Dept of Gastroenterology and Hepatology, Erasmus MC - University of Rotterdam, The Netherlands

14.40 Putative role for immunoglobulin-free light chain in inflammatory bowel disease and irritable bowel syndrome (p. 122)

A. Rijnierse[1], F.A. Redegeld[1], M.W. van der Heijden[1], B.R. Blokhuis[1], A.A. te Velde[2], I. Pronk[2], D.W. Hommes[3], J. Santos[4], M. Guilarte[4], F.P. Nijkamp[1], A.S. Koster[1], A.D. Kraneveld[1]. Div of Pharmacology & Pathophysiology[1], Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Center of Experimental Molecular Medicine[2], Dept of Gastroenterology and Hepatology[3], Academic Medical Center, Amsterdam, the Netherlands, Digestive Diseases Research Unit[4], Hospital General Vall d'Hebron, Autonomous University of Barcelona, Barcelona, Spain.

14.50 5-Aminosalicylic acid interferes with cell cycle progression of colorectal cancer cells (p. 123)
P.J. Koelink[1], M.A.C. Mieremet-Ooms[1], W.E. Corver[2], G. Griffioen[1], H.W. Verspaget[1]. Depts of Gastroenterology-Hepatology[1] and Pathology[2], Leiden University Medical Center, Leiden, The Netherlands.

15.00 Einde programma

Vrijdag 6 oktober 2006

Sectie Endoscopie Verpleegkundigen en Assistenten **Diezezaal**

Ochtendprogramma

10.00 – 10.30 uur	Ontvangst, koffie
10.30 – 10.50 uur	Bronchoscopie, patiëntencomfort en veiligheid *Mw. Drs. J. van Zwam, longarts-intensivist i.o., UMCN St Radboud, Nijmegen*
10.50 – 11.10 uur	48-uurs Ph-meting met Bravo capsule *Dhr. P.J.F. de Jonge, student, Erasmus MC, Rotterdam*
11.10 – 11.30 uur	De acute ulcus bloeding *Mw. Dr. M.E. van Leerdam, maag-darm-leverarts i.o., Erasmus MC, Rotterdam*
11.30 – 12.00 uur	Algemene ledenvergadering
12.30 – 14.00 uur	Lunchbuffet in de expositiehal

Middagprogramma

14.00 – 14.20 uur	Ontwikkeling van "Kwaliteitshandboek Flexibele Endoscopen Desinfectie" *Dhr. K. Ballemans, voorzitter stuurgroep Flexibele Endoscopen Reiniging en Desinfectie, UMCU, Utrecht*
14.20 – 14.40 uur	Een PEG-catheter plaatsen bij patiënten met ALS *Mw. Prof. dr. E.M.H. Mathus-Vliegen, maag-darm-leverarts, AMC, Amsterdam*
14.40 – 15.00 uur	Aanwezigheid van FAP in het duodenum *Mw. Dr. E Dekker, maag-darm-leverarts, AMC, Amsterdam*
15.00 uur	Koffie/thee, einde programma

09.30 – 10.00	Ontvangst koffie en thee
10.00 – 10.10	Welkomstwoord en inleiding

Nieuwe ontwikkelingen op MDL-gebied

10.10 – 10.40	Ontwikkelingen op gebied van behandeling tractus digestivus bloedingen *Dr. H.R. van Buuren, MDL- arts, Erasmus MC Rotterdam*
10.40 – 11.10	Gebruik van wormen bij de behandeling van de ziekte van Crohn *Dr. M.C.V.M. Russel, MDL-arts, Medisch Spectrum Twente*
11.10 – 11.30	*Ledenvergadering*
11.30 – 12.15	TIPSS (Transjugulaire Intrahepatische Portosystemische Stent Shunt) procedure bij ascites. *Prof. dr. J.P.H. Drenth, MDL-arts,* *UMC St. Radboud Nijmegen*
12.15 – 13.15	*Lunch*
13.15 – 13.45	Inhoud en implementatie SNAQ; een score instrument voor ondervoeding. *J. Nieuwhof, diëtiste, Maxima Medisch Centrum*
13.45 – 14.15	HIPEC: behandeling bij darmkanker *Mevr. Hermans, verpleegkundig consulent Antonius Ziekenhuis Nieuwegein*
14.15 – 14.45	Gebruik van pro biotica *Prof. dr. E. Claassen, hoogleraar cellulaire immunologie, Erasmus MC Rotterdam.*
14.45 – 15.00	Afsluiting

Relation between 18FDG-PET standardised uptake values and prognosis in oesophageal cancer patients

J.M.T. Omloo[1], M. Westerterp[1], R. Boellaard[2], O.S. Hoekstra[2], G.W. Sloof[3], J.J.B. van Lanschot[1]. Depts of Surgery[1] and Nuclear Medicine[3], Academic Medical Centre, University of Amsterdam and Dept of Nuclear Medicine and PET research[2], Free University Medical Centre, Amsterdam, The Netherlands

Oesophageal cancer still has an unfavourable prognosis due to its biological behaviour and specific therapeutic difficulties. Staging of oesophageal carcinoma is of great importance before an appropriate therapeutic strategy can be planned. Conventional staging methods such as endoscopic ultrasonography (EUS) or computed tomography (CT) still remain suboptimal because their accuracy rates are low when compared with surgicopathologic staging, and therefore do not correspond well with survival endpoints. Positron Emission Tomography (PET) is a non-invasive imaging technique which is increasingly applied in staging of different types of cancer. In addition to qualitative staging, PET is able to quantify 18F-FDG uptake in malignant tissue. The most commonly applied quantification parameter in clinical FDG-PET is the standardised uptake value (SUV). The aim of this study was to assess the potential (inversed) relation between SUV and survival in oesophageal cancer patients. Between October 2002 and August 2004 a prospective cohort study was performed. Eligible patients had histologically proven cancer of the thoracic oesophagus (type I) or the gastric cardia substantially involving the distal oesophagus (type II) without evidence of distant metastases or locally irresectable disease based on conventional preoperative work-up. In all patients who were considered eligible for potentially curative surgery, an oncological oesophagectomy was performed. Follow-up was complete until January 2006, ensuring a minimal potential follow-up of 16 months. The median SUV was 0.27 (range = 0 - 0.992) and was used for cut-off value between high (n = 32) and low (n = 31) SUV. Patients with a high SUV had a significantly worse disease free survival compared to patients with a low SUV ($p = 0.008$). In univariate analysis EUS N-stage ($p = 0.07$) and EUS tumour length ($p = 0.49$) were not related to disease free survival. However, EUS T-stage ($p = 0.03$) was associated with disease free survival. For multivariate analysis variables with a p-value <0.1 were entered (i.e. SUV, EUS T-stage and EUS N-stage). Among these variables SUV was the most potent independent prognostic factor ($p=0.06$). In surgically treated oesophageal cancer patients, SUV is the most potent predictor of disease free survival and can thus be of value when planning the most appropriate therapeutic strategy.

Patient preference for information on prognosis after potentially curative esophagectomy

S.M. Lagarde[1], ,J.R. van Werven[1], S.J. Franssen[2], E.M.A. Smets[2], H.C.J.M. de Haes[2], J.J.B. van Lanschot[1]. Depts of Surgery[1] and Medical Psychology[2], Academic Medical Center at the University of Amsterdam, The Netherlands

Esophageal cancer is an aggressive disease. After esophagectomy over 60% of patients still die of recurrence. In line with current notions, patients should be adequately informed about their disease status and prognosis. Therefore, the aim of this study was to identify factors which can predict preferences for information on prognosis in patients who underwent esophagectomy for cancer. A consecutive series of patients who underwent a potentially curative esophagectomy for cancer in the past two years and did not have cancer recurrence, received a questionnaire. Clinicopathological characteristics were prospectively collected. Information preference, sociodemographic characteristics, quality of life (EORTC QLQ-30), trust in doctors, anxiety and depression (HADS) were assessed using of a written survey. Multivariate analysis was used to assess independent predictors of information preferences.Of 109 eligible patients, 91 patients (83%) returned the survey. After surgery, 92% of patients wanted to know their general prognosis. Not wanting to know prognosis was not correlated with clinicopathological characteristics (e.g. age, tumor stage, complications), but was correlated with less trust in doctors ($p = 0.02$). 69% of patients were satisfied with the information given by the surgeon on the subject of general prognosis. The better the patients' physical functioning, the more satisfied ($p=0.03$). Only 76% wanted to know the chance of recurrence within one year. Not wanting to know was associated with less trust ($p = 0.03$) and more depression ($p = 0.02$). One third of patients (33%) did not want their doctor to initiate the discussion on prognosis, but preferred to start the discussion themselves or not at all. This was correlated with trust in doctors ($p = 0.03$): the less trust, the more the patient preferred to take the initiative. Additional information concerning prognosis was actively searched by 39 patients (36%). Conclusion: After esophagectomy for cancer most patients want to know their general prognosis. However, less people wanted this when substantiated in a timeframe. Interestingly, wanting to know prognosis was not correlated with clinicopathological factors, but with psychological factors such as depression and trust. About one third of patients did not want their doctor to initiate the discussion on prognosis. Future research is necessary concerning how to tailor the communication of prognosis to the individual patients' preferences

Role of (18)-FDG-PET-scan in preoperative management of oesophageal carcinoma.

C.A.S. Berende[1], C. Hoekstra[2], R.A.M.J. Claessens[2], K. Bosscha[1]. Depts of Surgery[1] and nuclear medicine[2], Jeroen Bosch Hospital, Den Bosch, The Netherlands

IntroductionThe (18F)-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scanning is a non-invasive, functional imaging technique. FDG exploits the native glucose transporters to enter the cell, many tumours have enhanced glucose uptake, FDG is readily accumulated in malignant cells and can be detected by a PET camera. This retrospective study deals with the diagnostic value of the PDG-PET scan in the preoperative work-up of oesophageal carcinoma. Patients and method From 2002 up to January 2006, 42 patients with histologically proven oesophageal carcinoma were retrospectively analysed. An X-ray, an oesophagogastroduodenoscopy with biopsy and CT-scan of neck/thorax/abdomen were done as conventional pre-operative screening methods. FDG-PET was added to all patients. Goal of the study was to evaluate if there is any change in management strategy. Results in eight (19%) out of 42 patients PDG-PET showed suspected lesions. Five patients (12%), all clinically classified as ASA III, had confirmed metastatic disease, four using an additional MRI or CT and one by thoracotomy. No oesophageal resection was performed in these patients. Three patients (7%) underwent laparoscopy and thorascopy, in which no suspected lesions were found. All three patients underwent oesophageal resection. During follow-up, these three patients presented with metastasis within 3,4 and 9 months.
Conclusion: FDG-PET improves the selection for surgery for oesophageal carcinoma when added to the conventional pre-operative screening methods and thus prevents unnecessary major surgery.

Liver Resection for Non Colorectal Metastasis

J. Kist[1], A.J.C. IJtsma[1], C.S. van der Hilst[2], A.S.H. Gouw[3], P.M.J.G. Peeters[1], R.J. Porte[1], K.P. de Jong[1], M.J.H. Slooff[1]. Dept of Hepatopancreatobiliary Surgery and Liver Transplantation[1] and depts of Medical Technology Assessment[2] and of Pathology[3], University Medical Centre Groningen, The Netherlands

The aim of this study is to evaluate the outcome of liver resections performed for non colorectal liver metastases (non-CRM) in terms of in-hospital mortality, morbidity, survival and disease free survival. From 1986 until 2004 data of 489 consecutive patients who underwent a liver resection, were collected in a prospective database. Of these patients, 23 underwent a liver resection for non-CRM. Our study population consisted of 14 female and 9 male patients with a median age of 52 (7-73) years. Comorbidity was present in 2 patients (8.7%). Statistical analysis was performed using Kaplan-Meier survival analysis, chi-square and Mann-Whitney-U testing where appropriate. Primary tumors leading to non-CRM were carcinoid (n=7), teratoma (n=3), schwannoma (n=2), gastro-intestinal stroma cell tumors (n=2), adrenal tumors (n=2), papillary thyroid carcinoma (n=1), endometrium carcinoma (n=1), ovarian tube carcinoma (n=1), renal cell carcinoma (n=1), granulosa cell tumor (n=1), leiomyoma (n=1) and ependymoma (n=1). Unilobar metastases were present in 15 patients and bilobar metastases in 8 patients. Nine patients had synchronous metastases versus 14 patients with metachronous disease. Liver resections were major (three segments of more) in 13 patients, minor (one or two segments) in 4 patients and local in 6 patients. Median blood loss was 1500 cc (100 – 8000). Median peroperative RBC transfusion was 0 units (0-11). R0 margins were achieved in 20 patients, whereas R1 or R2 margins were confirmed in 1 and 2 patients respectively. In-hospital mortality was 0%. Morbidity was observed in 8 patients (35%). One, three, and five year survival were 87, 73 and 64% respectively. One, three, and five year disease free survival were 86, 61 and 43% respectively. Comparing patients by gender, unilobar versus bilobar disease, neuro-endocrine versus non-neuro-endocrine tumor, synchronous versus metachronous metastases or by resection type showed no difference in survival ($p>0.05$). When the group of patients with non-CRM was compared to a group of patients with colorectal metastases, matched for gender, resection type, resection plane status and nodal status, no difference in overall and disease free survival could be observed.

In conclusion, patients with liver metastases from non-colorectal primaries can be resected with an acceptable outcome in terms of overall survival and disease free survival.

Clinical utility of COX-2 promoter hypermethylation in gastric cancer

M.F.G. de Maat[1,2], C.J.H. van de Velde[1], N. Umetani[2], P. de Heer[1], P.J.K. Kuppen[1], A.J. Bilchik[3], R.A.E.M. Tollenaar[1] and D.S.B. Hoon[2]. Dept of Surgery[1], Leiden University Medical Center, Leiden, The Netherlands, Dept of Molecular Oncology[2] and div of Gastrointestinal Surgery[3], John Wayne Cancer Institute, Santa Monica, CA, U.S.A.

In the Netherlands, yearly 1500 patients die of gastric cancer that has a 5-year survival rate of only 20%. Overexpression of cyclooxygenase-2 (COX-2) is present in 70-80% of gastric tumors and has been shown to enhance tumor progression and to effect survival. Epigenetic changes such as abberant methylation of gene promoter regions are found in gastric cancer. Promoter hypermethylation silences a target gene's expression and this effect is as significant as mutations, deletions or insertions. We investigated whether promoter hypermethylation of the COX-2 gene effects its protein expression and contributes to disease outcome in gastric cancer. We assessed the methylation status of COX-2 in primary gastric cancer tissue from all patients (n=56) accrued in the multi-center, randomized FAMTX trial (Dutch Gastric Cancer Group). Methylation-specific PCR was performed and COX-2 protein expression in primary tumors was evaluated by immunohistochemistry. Prognostic endpoints of analysis were time to recurrence, overall and disease-free survival and standard clinicopathologic features. COX-2 promoter hypermethylation was detected in 25% of primary gastric tumors. Tumors with lower expression of COX-2 showed increased levels of COX-2 promoter methylation. At a median follow-up of 51 months, patients with tumors showing COX-2 promoter methylation had significantly longer time to recurrence and overall survival in univariate (P=0.006 and P=0.03, respectively) and multivariate analysis (P=0.02, HR: 0.159, 95% CI: 0.036-0.702 and P=0.05, respectively).
Conclusions: The results suggest that promoter hypermethylation is an important regulatory mechanism of COX-2 expression in gastric cancer. Hypermethylation of the COX-2 promoter was identified as a favorable prognostic factor in gastric cancer in a trial-based population. The study suggests that specific inhibition of COX-2 may be useful in an (neo-) adjuvant treatment setting. Ultimately, absence of COX-2 promoter hypermethylation in the primary gastric tumor can potentially be used as a marker to identify a subpopulation of patients that would benefit from specific COX-2 inhibition.

Outcome after liver resection in the elderly

L.M.S. Boevé[1], A.J.C. IJtsma[1], C.S. van der Hilst[2], P.M.J.G. Peeters[1], R.J. Porte[1], K.P. de Jong[1], M.J.H. Slooff[1]. Dept of Hepatopancreatobiliary, Surgery and Liver Transplantation[1], Dept of Medical Technology Assessment[2], University Medical Centre Groningen, The Netherlands

The aim of this study is to assess outcome of liver resections in the elderly in a matched control analysis. The study population consisted of 100 patients aged 60 years or more at the time of liver resection. All patients were matched to a control patient aged under 60 years at the time of liver resection, with the same diagnosis and the same type of liver resection according to Coinaud segments. Both groups of patients were compared using preoperative characteristics like age, gender, type of disease and comorbidity. Outcome parameters were in-hospital mortality, morbidity, patient survival and disease free survival. Data were collected in a prospective database. Statistical analysis was perormed using Kaplan-Meier survival analysis, chi-square and Mann-Whitney-U testing where appropriate. Both groups consisted of 100 liver resections in 100 patients. Gender and type of disease were not different in both groups ($p>0.05$). Comorbidity was more often present in the elderly patients (31 vs 16%, $p=0.01$).Operative characteristics like magnitude of resection, blood loss, RBC transfusion, operation time and peroperative complication rate were not different ($p>0.05$). In-hospital mortality was higher in the elderly group of patients (11 vs 3%, $p=0.03$). Morbidity was also higher in the elderly group of patients (44 vs 27%, $p=0.01$). Patients with comorbidity had a higher rate of complications compared to patients without comorbidity (49% vs 31%, $p=0.03$). Reintervention rate, length of postoperative ICU stay and total hospitalisation time were not different comparing elderly and control patients and comparing patients with or without comorbidity ($p>0.05$). One, three, and five year survival rates in the elderly patients were 78, 51 and 37% respectively compared to 82, 48 and 34% respectively in control patients ($p>0.05$).One, three, and five year disease free survival rates in the elderly patients were 69, 47 and 40% respectively compared to 64, 34 and 29% in control patients ($p>0.05$).
In conclusion, despite a higher comorbidity rate and higher in-hospital mortality and morbidity rates in the elderly group of patients, outcome after liver resection in terms of survival and disease free survival are comparable between patients aged over 60 years and patients aged under 60 years.

Incidence and management of chyle leakage after pancreatoduodenectomy

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Background: Chyle leakage is a well-recognized complication following thoracic and abdominal surgery. Its incidence after pancreatoduodenectomy (PD) for suspected periampullary malignancy is unclear. The aim of this study is to review the literature and to describe incidence and management of chyle leakage following PD.
Methods: The aim of the present study was to evaluate incidence and management of chyle leakage after PD. Data was collected from a consecutive series of 518 patients who, in the period 1996-2005, had undergone PD for suspected malignancy. Patients who postoperatively developed chyle leakage, defined as having significant drain-output with 'milky' aspect and raised triglyceride (TG) levels (>1.2 mmol/L), were analyzed. Their management was reviewed.
Results: Of 518 patients, 111 patients (21%) were clinically suspicious for having chyle leakage. In 66 patients (12.7%) this was confirmed by TG level in drain output, while in 45 patients (8.7%) levels were too low or not determined. Chyle leakage was almost always identified between the 4-9 postoperative day. Early restoration of enteral feeding appeared to increase the incidence of chyle leakage. All patients were successfully treated conservatively with either Medium-Chain Triglyceride (MCT) diet, total parenteral nutrition or nil by mouth. After 2 days chyle leakage had resolved.
Conclusion: This study has described, among patients that underwent PD for a suspected malignancy, an incidence of chyle leakage of 12.7% that was confirmed by laboratory investigation, although clinically a higher number was suspected. Early introduction of enteral feeding encourages development. However, patients who develop chyle leakage remain clinically well and can be easily treated with dietary measures.

Effectiveness and morbidity of 68 needle catheter jejunostomies installed after major abdominal surgery.

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Introduction: Major abdominal surgery has an important impact on physiological changes of the gut. Therefore, enteral feeding is an important strategy for maintaining gut integrity and function. Feeding jejunostomy after major abdominal surgery is, however, still not widely accepted. This retrospective study analysed the morbidity of needle catheter jejunostomies (NCJ) placed after major abdominal surgery. Patients and method: Oesophageal resections, Whipple procedures, gastric resections and extended necrotectomies for infected necrosis of the pancreas (January 2002 to December 2005), in which 68 needle catheter jejunostomies were placed, were included. Principally, in all patients enteral nutrition was started the first post-operative day.
Results: Sixty-two patients (91 per cent) were successfully fed exclusively by NCJ postoperatively. Two patients (3 per cent) needed a re-exploration for a complication of the NCJ. In one case, the fixation of the NCJ showed a tenting with enteral nutrition pooled in the gut. The other patient had a bilioma around the insertion of the NCJ. The NCJ was removed and another NCJ was inserted without complications. One patient needed temporary total parenteraal feeding due to chylus leakage. Three patients had a paralytic ileus resulting in temporary less feeding via the catheter. No patients died due to complications of the NCJ.
Conclusion: NCJ feeding is an effective method of providing enteral nutritional support post-operatively with low morbidity.

Malpractice Litigation by Bile Duct Injury patients: associated factors for submitting a claim and the effect of the verdict on Quality of Life.

P.R. de Reuver[1], M.A. Sprangers[2], D.J. Gouma[1].Dept. of Surgery[1] and Medical Psychology[2], Amsterdam Medical Centre, Amsterdam, The Netherlands.

Bile duct injury (BDI) is associated with major patient morbidity, increased costs, impaired quality of life (QoL) and high rates of litigation claims from BDI patients. Studies from the United States showed the association between medical litigation and poor quality of life (QoL) in BDI patients. However it is not known which factors are associated with submitting a claim by BDI patients, and what the effect of the verdict is on QoL outcome. The aim of this study was to evaluate the factors associated with medical litigation in BDI patients and the effect of the verdict on QoL outcome. Of a total of 462 patients referred to our center between 1991 and March 2005, Quality of life was assessed in 403 eligible participants. The assessment was performed with a questionnaire containing the SF-36 and the GIQLI questionnaire. Additional questions were included, concerning the involvement in legal activity and if so the outcome of the verdict. Of the 278 patients (69%) who completed the questionnaire, 53 BDI patients (19%) reported involvement in legal activity and 225 (81%) patients reported no legal activity. The independent predictive factor for submitting a claim after cholecystectomy was a complete transsection of the common bile duct (odds ratio=7.5, 95% confidence interval =1.85-30.63). To date, litigation claims has been resolved in 38 cases (72%). Patients in whom the legal case was resolved in the patients favour through settlement or verdicts (n=17, 32%) scored significantly higher on the total GIQLI score (71±13,8 vs 57±20.6, P = 0.02).
Conclusion: Medical litigation claims are mostly submitted by patients with a complete transsection of the common bile duct. BDI patients involved in medical litigation report a poor QoL, but if the verdict was in the patient's favour, QoL scores significantly improve.

Acute appendicitis: a meta-analysis of test accuracy related to prevalence of disease

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Ultrasonography (US) and computed tomography (CT) are widely used in the diagnostic work up of acute appendicitis. Numerous studies have been performed evaluating both techniques, but which technique is preferable remains unclear. Purpose of this study was to perform a meta-analysis of head-to-head comparison studies on the value of US and CT in the diagnosis of acute appendicitis, with emphasis on accuracy among different prevalences of appendicitis. MEDLINE, EMBASE, CINAHL and Cochrane databases were searched from January 1966 to February 2006. Studies were included when fulfilling the following criteria: 1) prospective cohort design; 2) study population consisted of adults or adolescents; 3) comparison of US and CT, 4) surgery and/or clinical follow-up used as reference standard, and 5) data reported to calculate 2 x 2 contingency table. Estimates for positive and negative likelihood ratios for both US and CT were calculated based on a random effect model. Post test probability after CT or US is calculated for different prevalences as followed: post test probability = ((prevalence/1-prevalence) * LR) / 1+ ((prevalence/1-prevalence) * LR)Seven out of 393 studies met the inclusion criteria, evaluating 743 patients of whom 387 had appendicitis (50%). Positive likelihood ratio for CT and US were 7.6 (95%CI: 5.4-10.6) and 3.4 (95%CI: 2.5-4.7), respectively (p= 0.0025). Negative likelihood ratios were 0.20 (95%CI: 0.12-0.34) for CT and 0.35 (95%CI: 0.24-0.53) for US (p=0.023).In a patient population at the Emergency Department presenting with acute abdominal pain, with a 6% prevalence of appendicitis, positive CT and US results generate posttest probabilities of 33% and 15%, respectively, and negative CT and US generate posttest probabilities of 1% and 2%, respectively. While in a population with right lower quadrant pain or suspected appendicitis, with a 36% prevalence, these values were respectively 81%, 66%, 10% and 17 %. Conclusions: in head-to-head comparison studies, CT was found to be more accurate than US in the diagnosis of acute appendicitis. Accuracy of CT and US is highly dependant on prevalence, i.e. pretest probability. Acute appendicitis remains a diagnostic challenge and an optimal diagnostic strategy should be determined.

Emergency surgery for perforated diverticulitis: outcome after Hartmann's procedure or primary anastomosis of 217 cases

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Purpose: Although the incidence of diverticular disease has increased, perforated diverticulitis is not frequently observed. Mortality and morbidity rates of this acute complicated disease remain high. As there is a lack of randomized trials, the ideal treatment is still controversial. The object of this study was to compare the morbidity and mortality rates and length of hospital stay in four affiliated teaching hospitals in patients with perforated diverticulitis treated by resection with primary anastomosis (PA) and Hartmann's procedure (HP) in a multivariate analysis.
Methods: A multicenter retrospective study over a period of 16 years was carried out on 217 patients with perforated diverticulitis. Mortality and morbidity were compared between the HP group and the PA group with stratification for ASA classification, age, Mannheim Peritonitis Index (MPI) and Hinchey score.
Results: Multivariate analysis showed no significant difference in mortality between HP (30.5%) and PA (11.8%) (OR 1.9; 95% CI 0.8-4.7; p=0.172). In the HP group 31.9% of the patients needed reintervention to treat postoperative complications versus 14.5% in the PA group. This difference is still significant (OR 2.4; 95% CI 1.0-5.7; p=0.048) after stratification for Hinchey score, ASA classification and MPI. Besides, HP resulted in a longer total hospital and intensive care unit stay ($p<0.0001$ and p=0.002, respectively). Mortality and reintervention rate were not alleviated by a protective ileostomy in patients with PA.
Conclusion: PA for perforated diverticulitis with or without diffuse peritonitis can be safely performed, as morbidity and mortality rates are similar to those of HP. Besides, PA appears to be superior to HP in terms of major postoperative surgical complications that needed a reoperation or reintervention and total length of hospital stay.

A systematic review on the significance of extracapsular lymph node involvement in gastrointestinal malignancies.

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The presence and extent of lymphatic dissemination are among the most important predictors of survival in surgically treated gastrointestinal (GI) malignancies. The impact of extracapsular lymph node involvement (ECLI) has been studied for several malignancies, including GI malignancies. Aim of this study was to assess the current evidence on ECLI as a prognostic factor in GI malignancies.Medline was searched using a combination of keywords relating to ECLI in GI malignancies. Primary outcomes were incidence of ECLI and overall five-year survival rates. The literature search, quality assessment and data extraction were performed independently by two observers.Twenty-two manuscripts published between 1963 and 2006 were retrieved; eight were excluded because of an unclear definition of ECLI (n=6) or because they did not reported on ECLI. Fourteen manuscripts were included in the final analysis, six oesophageal, four gastric, one colorectal, and three rectal cancer series. There were only three prospective studies. In total, 2480 patients with lymph node positive GI malignancies were included. In these node positive cancers the incidence of ECLI ranged between 14-66% with no distinct differences between the different types of GI malignancies. Overall five-year survival rates for node positive oesophageal cancer without and with the presence of ECLI ranged between 33-53% and 12-23%, for gastric cancer between 45-85% and 5-26%, and for (colo)rectal between 62-81% and 30-44%, respectively. In the four studies that included also patients with node negative disease there was no, or only a modest difference in survival between node negative patients and patients with intracapsular lymph node involvement. A large survival difference in node negative patients compared to patients with ECLI was observed. In 10 of the 14 studies a multivariate analysis was preformed. In nine of them ECLI was identified as an independent risk factor for recurrence.
Conclusions: ECLI is a common phenomenon in patients with GI malignancies. It identifies a subgroup of patients with a significantly worse long-term survival. This systematic review highlights the importance of assessing ECLI as a valuable prognostic factor. Pathologists and clinicians should be aware of this clinically important feature.

Immunoglobulin-free light chains mediate the activation of mouse dorsal root ganglion neurons by antigens

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The immunoglobulin-free light chains (IgLC) secreted by B lymphocytes have been shown to mediate intestinal hypersensitivity by the induction of mast cell activation in an antigen-specific manner. Although both mast cells and sensory neurons contribute to the hypersensitivity response, the role of IgLC in relation to sensory neurons is unknown. We therefore aimed to investigate the effects of IgLC on murine cultures of dorsal root ganglion (DRG) neurons. Immunohistochemistry demonstrated that IgLC and IgE could specifically bind to murine cultured DRG neurons. Further, optical recordings showed that application of the corresponding antigen to IgLC- and IgE-sensitized DRG neurons induces a sustained increase in $[Ca^{2+}]_i$ in about half of these neurons. These results suggest that IgLC- and IgE-antigen complexes can act directly on mouse DRG neurons and reveal a novel potential pathway of antigen-specific neuronal activation in hypersensitivity responses.

Do drugs with anticholinergic properties increase the risk of reflux esophagitis? A study in a large Dutch GP database.

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Incompetence of the lower esophageal sphincter (LES) is a key factor in the pathogenesis of gastro-esophageal (GE) reflux disease. Drugs with anticholinergic properties may facilitate GE reflux by a relaxing effect on the LES. The aim of the study was to investigate whether the use of drugs with anticholinergic properties (inhalation anticholinergics, antipsychotics and tricyclic antidepressants) is associated with an increased risk of reflux esophagitis.A population-based case-control study was conducted within the Integrated Primary Care Information database over the period 1996-2005. Cases with endoscopy confirmed esophagitis were identified and each matched with 10 controls on gender, age, GP practice and calendar time. Exposure to anticholinergic drugs was assessed in the year before diagnosis and categorized as current (last prescription covered or ended within 1 month prior to the index date), past and no use. Current users were further categorized according to the Defined Daily Dose (DDD)/day of their last prescription. The relative risk of reflux esophagitis was estimated by adjusted odds ratios (OR) with 95% confidence intervals (95% CI) using conditional logistic regression analysis.During the study period, 1,462 cases with endoscopy-proven esophagitis were identified and 13,462 controls were matched. The risk of reflux esophagitis was elevated in current (OR: 1.48, 95% CI: 1.09-2.00) and past (OR: 1.66, 95% CI: 1.25-2.19) users of drugs with anticholinergic properties. The risk was highest among current users using >1 DDD/day (OR: 1.79, 95% CI: 1.08-2.96). Users of tricyclic antidepressants were most likely to develop reflux esophagitis (OR: 4.18, 95% CI: 1.62-10.79 for current users using >1 DDD/day). In persons using tricyclic antidepressants for neuropathic pain rather than depression the risk was elevated as well (OR 2.58, 95% CI 1.09-6.10 for current users), which suggests that a depressive state by itself does not play an intervening role in the observed association.
Conclusions: The use of drugs with anticholinergic properties is associated with an increased risk of reflux esophagitis development. This effect was strongest in users of tricyclic antidepressants.

The effect of oral administration of ursodeoxycholic acid and proton pump inhibitors in patients with Barrett's esophagus.

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Bile acids may play a role in the pathogenesis of Barrett's esophagus (BE). Bile composition can be influenced by oral administration of ursodeoxycholic acid (UDCA). We prospectively investigated the effect of proton pump inhibitors (PPI) supplemented with UDCA in vivo in patients with BE. Pts with no or low-grade dysplasia who were clinically asymptomatic on PPI were eligible for the study. In order to exclude the effects of acid reflux, all pts were initially treated with 40 mg esomeprazol (ESO) BID for six mo and continued on this dose till the end of the study (t=12 mo). During a period of six months (t=6 mo - t=12 mo) pts were treated with oral UDCA (600 mg BID). Pts underwent endoscopy at t=0 mo, t=6 mo & t=12 mo with multiple biopsies of the distal and proximal BE segment, normal squamous and gastric cardia. In addition, pH was measured at t=0 mo & t=6 mo using a BRAVO wireless pH capsule and bile was sampled at the beginning of the UDCA treatment and six mo later (t=6 mo & t=12 mo). All biopsies were reviewed for the extent of metaplasia, dysplasia, and acute & chronic inflammation. In addition proliferation (Ki67), differentiation (villin, cytokeratins 7 & 20) and inflammation (COX-2) were investigated by immunohistochemistry (IHC). Nine pts (mean age 60 yrs, median BE length 7 cm) were included, 3 with low-grade dysplasia. pH measurements revealed a normalisation of the intraesophageal pH at t=6 mo (t=0: 4% vs. t=6: 2% fraction time pH<4). In addition, bile composition analysis demonstrated the efficacy of UDCA (UDCA % in bile t=0:0, t=6:0.5, t=12: 45). Combining the results of both phases of the study, no significant changes were seen in any of the histological & IHC parameters (chronic inflammation (0-3 score) t=0 = t=6 = t=12:2, acute inflammation (0-3 score) t=0 = t=6:0, t=12:1). In 5 patients the amount of metaplasia and dysplasia was marginally increased, mostly pronounced distally (metaplasia (1-3 score) t=0 = t=6:2, t=12:3, dysplasia (0-4 score) t=0 = t=6:0, t=12:1). Differentiation and proliferation parameters showed no significant changes (differentiation (0-3 score) t=0 = t=6 = t=12:2, proliferation (0-3 score) t=0 = t=6 = t=12:1).

Conclusion: In this study, in BE pts who were clinically asymptomatic on PPI, increasing the PPI dose to the maximum for six mo followed by the addition of UDCA for six mo did not result in significant histological or IHC changes in their BE.

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The most optimal strategy to detect distant metastases in patients with esophageal cancer

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Computed tomography (CT) of neck, thorax and abdomen is presently the standard procedure to detect metastases in patients with esophageal cancer. It is not clear whether other investigations, i.e., ultrasound (US) abdomen, US neck, and chest x-ray (CXR) should also be performed. In this study, we determined the additional diagnostic value of these investigations.In 569 esophageal cancer patients who had undergone CT and one or more other investigations, i.e., US abdomen, US neck and/or CXR, results were compared with the gold standard based on surgery, biopsy or follow-up. Combined results of CT with US abdomen, US neck, and CXR, respectively, were considered positive for metastases in a region if: a) at least one of the investigations performed in a region was positive (OR-group), or b) two investigations performed in a region were positive (AND-group). Sensitivities and specificities were determined at the organ and the patient level. According to gold standard, 58, 75, 26 and 19 patients had metastases in supraclavicular nodes, celiac nodes, liver or lung, respectively.At the organ level, sensitivity of CT was higher for celiac lymph nodes, liver and lung metastases than US abdomen or CXR. Sensitivity of US neck was higher for supraclavicular nodes than CT. At the patient level, sensitivity for distant metastases was 66% and specificity was 95% if only CT was performed for all regions. A higher sensitivity (86%) was achieved when US neck (OR-group) was added for supraclavicular nodes (with CT for the other regions), at the same specificity (95%). Sensitivity and specificity remained equal when US abdomen or CXR were added to detect metastases, using the assumption that at least one investigation had to be positive (OR-group). A slightly higher specificity of 97% was achieved by the addition of US abdomen for liver metastases, when the assumption was made that both CT and US abdomen had to be positive for a positive result (AND-group). Sensitivity however declined in this scenario.
Conclusion: The highest sensitivity for detecting distant metastases was obtained with the combination CT and US neck in patients with esophageal cancer. For a slightly higher specificity (less false positives) US abdomen could be added, but only using the assumption that both CT and US abdomen had to be positive for the presence of liver metastases (AND-group). The consequence of this would however be that the sensitivity declined, which may clinically not be desirable.

Test first or treat first? A randomized comparison of treatment strategies for dyspepsia.

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The aim of this study was to compare two treatment strategies consisting of multiple treatment steps, one starting with an H. pylori test, the other saving H. pylori testing for patients with relapsing symptoms.Patients referred by their general practitioners for evaluation of dyspeptic symptoms without recent endoscopy or H. pylori test were randomized to one of the following treatment strategies combining triple therapy (esomeprazole 20mg, clarithromycin 500mg, amoxicillin 1000mg, all b.i.d. for 7 days), and esomeprazole therapy (40mg once daily for 4 weeks):"Test first": ^{14C} urea breath testing and triple therapy (if Hp+) or esomeprazole therapy (if Hp-), in case of persisting/relapsing symptoms followed by esomeprazole therapy; "Treat first": esomeprazole therapy, in case of persisting/relapsing symptoms followed by ^{14}C urea breath testing and triple therapy (if Hp+) or esomeprazole therapy (if Hp-).Primary outcome was the proportion of symptom-free patients 6 months after randomization. Secondary outcomes were the proportions of patients who felt adequately treated at 6 months, who were symptom-free after the first treatment step, with symptom-relapse, and using dyspepsia related medication at 6 months.Ninety-two patients were included in the "test first" strategy (mean age 43 years, 39% male, 57% H. pylori positive), 90 in the "treat first" strategy (mean age 45 years, 41% male, 51% H. pylori positive). After the first treatment step, 50 (54%) "test first" patients and 42 (47%) "treat first" patients were symptom-free (p=0.18). In these patients symptom relapse was more common in the "treat first" strategy (79% vs. 43%, p<0.001) and these patients had a second course of empirical treatment. At 6 months, 49 (53%) "test first" patients were symptom-free, compared to 43 (48%) "treat first" patients (p=0.46), while 72 (78%) of the "test first" patients and 74 (82%) of the "treat first" patients reported that they felt adequately treated, and 29 (32%) vs. 28 (30%) used proton pump inhibitors (p=0.95). Overall, only 17 (9%) of patients had endoscopy.
In conclusion, both empirical treatment strategies were equally effective for treatment of patients with dyspeptic symptoms, but the test first strategy seemed preferable due to the lower relapse rate. Although, only half of the population was symptom-free after 6 months, the majority of patients felt adequately treated, and only few patients had endoscopy.

High prevalence of intraepithelial lymphocytosis (Marsh I and II) in duodenal biopsies in a large cohort of patients referred for routine gastroduodenoscopy

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Histologically, celiac disease is characterised by a triad of villous atrophy, crypt hyperplasia and increased intra-epithelial lymphocytes (IELs). In recent years, it has been recognised that total villous atrophy is no prerequisite, but milder villous atrophy may indicate celiac disease as well. Moreover, it has been shown that increased IELs without atrophy may respond to gluten as well: some subjects developed overt celiac disease after gluten challenge, while other studies reported resolution of dyspeptic symptoms in 10-40% of patients after gluten free diet. The prevalence may depend on the group studied, and specific T-lymphocyte staining. To establish the prevalence of duodenal IEL increase in symptomatic patients referred for gastroduodenoscopy using CD-3 staining and histomorphometry. From 1997 on, we routinely took 3-4 duodenal biopsies in patients referred for either suspected celiac disease, or patients with diarrhea, anemia, weight loss or severe dyspepsia. The duodenal biopsies were stained with haematoxylin/eosin (HE) and scored for the presence of villous atrophy, crypt hyperplasia and IELs. Unless these were completely normal, an immunohistochemical staining of CD-3 positive lymphocytes was performed, followed by IEL count (expressed as lymphocyte count / 100 epithelial cells). A cut-off of 30 IEL / 100 was chosen. The biopsies were classified according to Marsh. From January 1997 to september 2005 a total of 30.564 gastroduodenoscopies were performed. In 3454 patient (11%) duodenal biopsies were taken. In 2396 (69,4%) patients the mucosa was normal, 792 patients (22,9%) had a Marsh I lesion, 116 patients (3,4%) Marsh II, and 150 (4,4%) patients had villous atrophy (Marsh IIIa-c). We conclude that using CD-3 specific staining and upholding a low threshold for taking duodenal biopsies resulted in a high proportion of patients with increased IELs. The high prevalence in this study of symptomatic patients with Marsh I or II lesions underscores the need for prospective studies to assess the value of gluten free diet in these patients.

Post-absorptive plasma citrulline levels fail to discriminate healthy controls from patients with malabsorption due to severe villous atrophy

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Recently, attention was drawn to the nonprotein amino acid citrulline for its ability to reflect enterocyte mass in various small intestinal disease states in humans. Since the small bowel is the main source of circulating citrulline, it is hypothesized to be an attractive marker of enterocyte mass or enteral (dys)function.
This study compared post-absorptive plasma citrulline levels and the intestinal absorption capacity in healthy controls and patients with known decreased enterocyte mass/function due to severe villous atrophy.
The objective was to determine whether post-absorptive citrulline levels could discriminate between subjects with normal small bowel absorption and patients with known malabsorption caused by severe villous atrophy (Marsh 3+).
Fasting state venous citrulline levels were collected in both healthy controls and patients. Citrulline analysis was performed by high performance liquid chromatography. Fecal energy loss was assessed by bomb calorimetry of 3-days faecal output and subsequent caloric intake using a 4-days nutritional diary. Intestinal absorption capacity was calculated as the difference in caloric intake and faecal loss expressed as percentage.
Fourteen healthy controls (11F, 3M) had a mean age and BMI of 38.5 ± 13.1 years and 23.3 ± 2.1 kg/m^2, respectively. Six patients (4F, 2M) with severe villous atrophy due to refractory coeliac disease had a mean age and BMI of 61.2 ± 6.0 years and 20.6 ± 1.6 kg/m^2, respectively.
Mean post-absorptive plasma citrulline levels were 36.0 ± 8.9 and 30.2 ± 8.7 μmol/L (p=0.14) in healthy controls and patients with severe villous atrophy, successively. Mean intestinal absorption capacity was 89.6 ± 4.5 and 81.4 ± 14.2% (p=0.25), mean faecal energy loss was 217 ± 80 and 578 ± 410 kcal/day (p=0.02) in healthy controls and patients with severe villous atrophy, respectively. Post-absorptive plasma citrulline levels fail to discriminate healthy controls from patients with malabsorption or increased faecal energy loss due to severe villous atrophy, as indicated by the overlap in citrulline levels between these two groups (Rs = 0.37, p=0.11). In conclusion, post-absorptive plasma citrulline levels could not discriminate healthy controls from patients with malabsorption due to severe villous atrophy. Post-absorptive plasma citrulline levels citrulline levels are insufficient as a marker of entorocyte mass and function.

Cholestatic bile salt concentrations do not affect proliferation or differentiation of intestinal epithelial cells *in vitro

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Introduction: Bile salts have been implied in the induction of proliferation and apoptosis in many different cell lines. It is unclear, however, whether bile salts in compositions and concentrations found in cholestasis affect the proliferation, differentiation or apoptosis of small intestinal epithelial cells. Compromised differentiation of the intestinal epithelium could provide an additional pathophysiological mechanism for the frequently encountered compromised nutritional status during cholestasis.
Aim: To determine whether cholestatic bile salt concentrations affect proliferation, differentiation or apoptosis of intestinal epithelial cells *in vitro*.
Methods: Human colon carcinoma cells, Caco-2, which feature a small intestinal phenotype upon confluency, were exposed to bile salts in cholestatic concentrations and compositions (molar ratio; GCA:TCA:GCDCA:TCDCA, 2:2:1:1; concentration range 0-450 μM), either in the proliferative or in the differentiated stage. Proliferation was determined by analyzing cell growth, protein and DNA synthesis, and expression of the cyclin-dependent kinase inhibitors p21 and p27. Apoptosis was determined by analyzing caspase-3 activity. To determine the effect on differentiation, mRNA and activity levels of sucrase-isomaltase and lactase, two enzymes involved in carbohydrate hydrolysis, were quantified. Additionally, mRNA levels of their upstream intestine-specific transcription factors were measured. A LDH assay was performed to determine possible cytotoxicity of the bile salts.
Results: The conjugated bile salts did not affect cell growth, protein and DNA synthesis, or p21 and p27 expression. Caspase-3 activity was not affected by cholestatic bile salts in either proliferating or differentiated cells. No difference was observed in the expression of the genes coding for the intestinal transcription factors Cdx2, GATA-4 and HNF-1α, or of their downstream genes coding for sucrase-isomaltase and lactase. Sucrase and isomaltase activities of control and bile salt-treated cells were virtually identical. The LDH assay confirmed that the bile salts were not cytotoxic to the Caco-2 cells.
Conclusions: Intestinal mucosal cells are resistant to bile salts in cholestatic concentration and composition. The conservation of small intestinal function during cholestasis opens up possibilities for optimalization of the nutritional condition.

Folate and colon cancer
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Folate is an important vitamin (vitamin B11) that is present in vegetables, milk and other foods. To investigate the effect of folic acid on colon cancer a multidisciplinary approach has been used. In an observational case-control study, we evaluated the association between the intake of folate, vitamin B2, B6 and B12 intake and the occurrence of colorectal polyps. Among those with the highest folate a slightly increased risk of polyps was observed as compared to subjects with lower folate intake, especially for those with low intake of vitamin B2. Thus, the expected protective effect was not confirmed in this study and a balanced intake of B-vitamins seems advisable. In a 6 month human intervention study among individuals with previous colorectal polyps, the effects of a high dose folate and vitamin B12 supplementation was compared to placebo. An increase in uracil misincorporation and promotor methylation was observed. This provides a possible indication for an increase risk of neoplastic formation, rather than a beneficial effect of folate supplementation, especially for those susceptible to colorectal cancer. In a nutrigenomics analysis of human colon cancer cell lines, effects of folate were examined using DNA microarrays. Iron metabolism was found to be affected and lowering of iron status was confirmed. Also in the human intervention study, lowering of iron status was seen, not in colon, but in blood. Therefore, high dose supplementation with folic acid should be accompanied with iron. Finally, our in vitro studies showed different effects of supplemental doses of synthetic folic acid and natural methyltetrahydrofolate. Additional research is required to determine whether folic acid is the preferential form of supplementation.
In conclusion: our results increase the doubt on general fortification with folic acid, especially in view of possible adverse effects on colon cancer risk.

Prevalence of abdominal symptoms in recreational runners competing in a long-distance run: an observational study in 1281 subjects

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Gastrointestinal (GI) symptoms are reported in up to 70% of endurance top-athletes. No data about the prevalence in recreational runners are available. Furthermore, it is unknown whether abdominal complaints are an important reason to abandon a race. We investigated the prevalence of GI complaints during and after a long-distance run. We were specifically interested in the occurrence of abdominal and systemic symptoms possibly related to GI-ischemia, reperfusion damage or endotoxemia. A questionnaire was sent to all available email addresses of athletes who had competed in a popular recreational run. We evaluated the records of the 10, 21, and 42 kilometres running distances. 3521 runners started the race (10 km, n=1017, 21 km, n=1978 42 km, n=526). Email addresses of 2076 subjects were available, 1281 (62% response rate) were returned (10 km n=261, 21 km n=767, 42 km n=228). The run was completed by 98% of the runners. Twenty-six athletes dropped out, of whom 3 did so because of GI-symptoms (0.2%).Abdominal complaints during the run were reported by 53%: the most important complaints were side stitch (19%), flatulence (14%), sickness or vomiting (10%), urge to defecate or diarrhoea (9%). Statistical analysis revealed a significant correlation between severity of abdominal complaints during running and female sex ($r=0.16$, $p<0.0001$), younger age ($r= -0,14$, $p<0,001$) and less running experience ($r=-0.05$, $p=0.04$). In the recovery period, within 24 hours after running, 13% had abdominal complaints, consisting of sickness and/or vomiting (6%), shivering (5%), diarrhoea (5), collapse (2%) and bloody stools (1%). There was a significant correlation between the severity of post-exercise abdominal complaints and female sex ($r=0.16$, $p<0.0001$), abdominal complaints during running ($r=0.19$, $p<0.0001$) and running distance ($r=0.05$, $p=0.04$) GI-symptoms have a high prevalence in recreational runners but are seldom the main reason to abandon the race. The relation between post-exercise complaints and abdominal complaints during the race and running distance, may indicate reperfusion damage and endotoxemia. This suggests that GI-ischemia plays a role in the pathophysiology of exercise induced abdominal complaints.

Atherosclerotic risk factors in patients with chronic splanchnic syndrome

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There are no epidemiological studies describing atherosclerotic risk factors in patients (pts) with chronic splanchnic syndrome. Aim of this study was to describe atherosclerotic risk factors in pts with atherosclerosis and chronic splanchnic syndrome.
Methods: From 1997 until october 2005, 530 pts were nationwide referred for suspected gastrointestinal ischemia. All underwent a standard work-up including full medical history, physical examination, duplex-ultrasound, splanchnic angiography and gastric exercise tonometry. In patients with splanchnic atherosclerosis, extensive laboratory evaluation for atherosclerotic risk factors was performed. In 168 pts the diagnosis chronic splanchnic syndrome (CSS) was made. In 57/168 crural compression of a normal vessel was found, 111 had atherosclerotic splanchnic disease. In 36 pts laboratory testing was incomplete. We evaluated atherosclerotic risk factors in 76 pts (58 F, 18 M, mean age 61 (range 28-86). Single-vessel disease was present in 21 pts, 2-vessel in 45, and 3-vessel in 10 pts.
Results: A family history of coronary heart disease was seen in 68%.
Concomitant disease: in 43% coronary artery disease was present, in 38% peripheral vascular disease. Hypertension was present in 68%, hypercholesterolemia in 43%. Diabetes was present in 15%, thyroid dysfunction in 9% (hypothyroidism in 4% and hyperthyroidism in 5%). Nicotine use was seen in 57%. Venous thrombosis was present in 1,4%, a history of rheumatologic disease in 7% . Overweight (defined as BMI> 24) was seen in 31%.
Laboratory testing: abnormal thyroid function in 1,3%, elevated fasting homocystein (>15 µmol/l) in 45%. The cholesterol at referral was mean 4,5 mmol/l (SD 1,3) HDL-cholesterol: 1,2 mmol/l (SD 0,48) LDL-cholesterol: 2,4 mmol/l (SD 1,17), triglycerides: 1,3 mmol/l (SD0,86). Renal function (creatinine clearance < 30 ml/min) was abnormal in 8%.
Conclusions: Most risk factors for splanchnic atherosclerosis are similar to those known for general atherosclerosis, including a family history of coronary heart disease, concomitant coronary artery and peripheral vascular diseases, hypercholesterolemia, hypertension and nicotine use.
Two differences with other vascular beds were found: the striking female preponderance, in concordance with previous studies in CSS, and the high incidence of elevated fasting homocystein. These risk factors should be taken into account when evaluating a patient with unexplained abdominal pain.

Haemorrhoid Artery Ligation (HAL) for second to fourth degree haemorrhoids - a pilot study

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Haemorrhoids result from the pathological changes in prolapsed anal cushions. Symptoms include bright red bleeding, prolapse and sensation of incomplete evacuation, soiling and itching. There are several outpatient treatments, such as rubber band ligation, sclerotherapy and infrared coagulation. For bigger haemorrhoids, operative haemorrhoidectomy is still the most common treatment. Disadvantages are the postoperative pain and complications as urine retention, bleeding, anal stenosis, infection and incontinence. New therapies with less morbidity and complications are sought. A new therapy is the Haemorrhoid Artery Ligation (HAL) procedure, where haemorrhoidal arteries are identified with Doppler sound and consecutively selectively ligated. In our study, the effect of the HAL-procedure was evaluated in patients with second to fourth degree haemorrhoids. From January 2005 until August 2005, 61 consecutive patients (41 male, 20 female) with symptomatic second to fourth degree haemorrhoids were treated in our hospital with HAL under spinal anaesthesia in day care. Median age was 49 (20-81) years old. Two different HAL instruments were used; THD (Endomed) and AMI HAL Doppler (The Surgical Company).After a median follow-up of 7 (3-11) months 46 from 61 patients (75%) were symptom free. In 7 patients (12%) symptoms had improved > 50% and in 8 patients (13%) treatment had no effect. There were no differences between both instruments used. Healing percentages for second, third and fourth degree haemorrhoids were 70%, 90% and 65%, respectively. Complications were bleeding postoperatively in 5 patients (8%), urine retention in 2 patients (3%) and severe anal pain in 1 patient (2%). Rehospitalization was needed in 6 cases, 5 for bleeding postoperatively and 1 for severe anal pain. The recurrence rate was 2/61 (3%).
Conclusion: HAL is an effective treatment for second to fourth degree haemorrhoids. After 1 treatment 75% is symptom free and in 12% symptoms have improved. It is a minimally invasive day care technique, with less complications and morbidity than classical haemorrhoidectomy and it does not compromise future treatments.

A transcription-based copper sensor enables analysis of copper homeostasis in living cells

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The transition metal copper is an essential trace element, but an excess of copper is very toxic. Systemic copper levels are therefore tightly controlled by hepatic copper excretion into bile. This is carried out by the hepatic copper transporter ATP7B, which is mutated in patients with Wilson disease. A lack of copper excretion results in chronic copper overload in the liver of these patients, ultimately resulting in liver cirrhosis. Mutations in the homologous copper transporter ATP7A result in a fatal neurodevelopmental disorder called Menkes disease. Early diagnosis of these severe copper disorders is essential for adequate treatment. Unfortunately, radioactive copper assays are currently the only way to study copper homeostasis in a cell. The applicability of this method is rather limited due to the short half-life of the radioisotope. Our aim was to develop and validate a transcription-based copper sensor, based on a cell-intrinsic mechanism to sense copper and induce adaptive responses. High cellular copper levels are detected by the transcription factor MTF-I, which induces transcription of metallothionein genes to scavenge an excess of copper. We engineered a firefly luciferase reporter construct containing four metal responsive elements (MREs) from the promoter region of the murine metallothionein I gene. In this way, MTF-I driven transcription induces firefly luciferase expression. Copper and zinc, but not iron induced our reporter in a concentration- and time-dependent manner when transiently transfected into HEK 293T cells or HELA cells. These metal concentrations are within a sublethal range as measured by MTT viability assays. Similar copper concentrations result in relocalization of ATP7B from the trans Golgi-network to the cell periphery. Interestingly, induction of our reporter was completely abolished by the concomitant overexpression of ATP7B, but not by overexpression of a catalytic null mutant of ATP7B (D1027A). Expression of ATP7B with a Wilson disease-associated missense mutation G85V partially abolished the induction of the reporter. Taken together, these data establish our reporter as a sensitive and versatile metal sensor in living cells and confirm the known function of ATP7B in copper excretion. This reporter may represent a useful tool to aid in the diagnosis of copper homeostasis disorders. Finally, these are the first data that reveal a direct competition between ATP7B and metallothioneins for the same cellular copper pool.

Peroxisome proliferator-activated receptor α (PPARα) is an important determinant of hepatic carbamoylphosphate synthetase I (CPS I) expression, both *in vitro* and *in vivo.*

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Carbamoylphosphate synthetase I (CPS) is the rate-limiting enzyme of the urea cycle, in which toxic ammonia is converted to urea. It previously has been shown that glucocorticoids and glucagon, the latter via cAMP, are important factors in the regulation of hepatic CPS expression. Via the transcription factors GR and CREBP respectively, they induce CPS expression. CPS is expressed in hepatocytes in a declining portal to central gradient. Due to the like modularity of the CPS enhancer and the enhancers of other periportally expressed genes, CPS may act as a general model for the regulation of these genes. Recently it became clear that the transcription factor PPARα is an inhibitor of hepatic CPS expression. There is however no perfect PPAR-RE present in the upstream regulatory DNA sequence of CPS.
The aim of this study is to identify the sequence in the CPS regulatory DNA sequence that is responsible for the inhibitory effect of PPARα, to establish whether this inhibition is a direct or indirect effect, and to identify putative interactions between PPARα and other transcription factors e.g. GR.
To determine the *in vitro* effect of PPARα we performed transfection assays using CPS-luciferase reporter constructs. To determine the *in vivo* effect of PPARα we either crossed CPS-luc reporter mice with PPARα$^{-/-}$ mice or administered the PPARα ligand WY14643 to these reporter mice.
The *in vitro* data show that a CPS enhancer region of 469 bp is sufficient to confer PPARα responsiveness to a luciferase reporter construct and that, depending on the concentrations of the glucocorticoid dexamethasone and the PPARα ligand WY14643, PPARα may act as an inducer or inhibitor of CPS expression. The *in vivo* data show that both endogenous CPS expression as well as the luciferase reporter gene are induced in PPARα$^{-/-}$ mice. The downregulation of both upon administration of WY14643 to the CPS-luc reporter mice indicates that this is a direct effect of PPARα.
Conclusions: we have shown that PPARα is an important determinant of CPS expression both *in vitro* and *in vivo*. We are currently investigating if PPARα binds directly to the 469 bp CPS enhancer, what the interactions between PPARα and other transcription factors are and, last but not least, whether PPARα is a common regulator of periportal gene expression.

COMMD proteins as a novel family of regulators of copper homeostasis

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The copper transporting P-type ATPases ATP7A and ATP7B play a pivotal role in copper homeostasis. Dysfunction of ATP7A or ATP7B causes disorders characterized by copper deficiency (Menkes disease) or copper overload (Wilson disease) respectively. Recently, we established that COMMD1 (previously MURR1), a protein that when mutated causes copper toxicosis in Bedlington terriers, interacts with ATP7B. COMMD1 has nine human homologues that share a novel conserved motif known as the copper metabolism gene MURR1 (COMM) domain. In the present study the interaction between COMMD1 and ATP7B was further characterized, and the potential role of other COMMD proteins in copper homeostasis was investigated through the study of protein-protein interactions with copper transporting P-type ATPases. Interaction of COMMD1 with ATP7B is mediated through the amino-terminus of ATP7B. Although this region contains six tandem copper binding sites, the interaction of ATP7B with COMMD1 is insensitive to copper. Several Wilson disease causing mutations in this region of ATP7B are associated with increased binding to COMMD1, suggesting that alteration of this interaction plays a role in the pathogenesis of Wilson disease. Three COMMD proteins other than COMMD1 interact with ATP7B. In addition, seven COMMD proteins, including COMMD1, were identified as novel interacting partners for ATP7A. These data indicate that COMMD proteins form a novel family of putative regulators of copper homeostasis, and could thus have a role in human disorders of copper homeostasis.

Increased activity of hypoxia-inducible factor 1 leads to early embryonic lethality in Commd1 null mice

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We recently established that a loss-of-function of the COMMD1 protein, due to a homozygous exon 2 deletion of the *COMMD1* gene, (previously known as *MURR1*), is associated with autosomal recessive copper toxicosis (CT) in Bedlington terriers. This disorder is characterized by an inefficient excretion of copper via the bile, resulting in progressive accumulation of hepatic copper, which leads to chronic hepatitis and ultimately liver cirrhosis. COMMD1 interacts with ATP7B, the copper transporting P-type ATPase mutated in Wilson disease, a hepatic copper overload disease in man similar to canine CT. COMMD1 is the prototype of the recently defined protein family the Copper Metabolism gene MURR1 Domain (COMMD) proteins. Besides the established role of COMMD1 in copper homeostasis, identified protein-protein interactions also implicate COMMD1 in the regulation of sodium transport and NF-kB signalling. To elucidate the function of Commd1 *in vivo* we targeted the murine *Commd1* gene in embryonic stem cells and generated heterozygous *Commd1* null mice. *Commd1+/-* mice are born healthy and do not show a distinct phenotype compared to wild-type mice, whereas homozygous *Commd1* null mice have an embryonic lethal phenotype. *Commd1-/-* mice die between 9.5 and 10.5 dpc. Although COMMD1 is associated with copper homeostasis in mammals, no direct evidence for dysregulated copper homeostasis was observed in *Commd1-/-* embryos. The embryonic development of *Commd1-/-* mice was general retarded and vascularization of the placenta did not occur in *Commd1-/-* embryos. Microarray analysis identified transcriptional upregulation of hypoxia-inducible factor 1 (HIF-1) target genes in 9.5 dpc *Commd1-/-* embryos compared to normal embryos. Upregulation of HIF-1 target genes was caused by an increase of HIF-1α protein levels in *Commd1-/-* embryos. These results indicate that Commd1 is critical for normal mouse embryonic development, which is in contrast to the CT phenotype in COMMD1 deficient dogs. It appears that embryonic lethality is caused by dysregulated HIF-1 activity that has been shown to be very essential for normal embryonic development. Using a conditional *Commd1* knockout mouse we started to further elucidate the role of Commd1 in embryonic development and in hepatic copper homeostasis in life born mice.

A Specific Intestinal Cholesterol Secretion Pathway Contributes to Cholesterol Removal

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Traditionally, hepatobiliary cholesterol (CH) excretion is supposed to be the only way to excrete substantial amounts of CH from the body. However, CH balance studies have shown that more neutral sterols are present in feces than can be explained by hepatobiliary excretion. Indeed, our mouse models with abrogated biliary CH secretion and show that a substantial amount of the daily excreted CH is derived from the intestine. In vivo experiments in which the intestine was perfused further indicate the existence of a specific intestinal cholesterol efflux pathway. Such a pathway provides a very attractive target to increase the rate of reverse cholesterol transport.
Our objective is to characterize the pathways responsible for this direct trans-intestinal transport. To discern whether TG-rich lipoproteins may directly be involved, we intra-venously injected C57Bl/6 mice with chylomicron-mimicking TG-rich emulsion particles containing either ^{3}H-cholesteryl oleate (^{3}H-CO) or cholesteryl oleyl ether (^{3}H-COEth), which is resistant to intracellular hydrolysis. Two hours after injection the proximal small intestine (10 cm) was canulated and perfused for 90 min with buffer containing taurocholate/lecithin (10mM:2mM). Both ^{3}H-CO and ^{3}H-COEth-labeled emulsion particles were rapidly cleared from the circulation (t ½ ≤ 5 min), and mainly taken up by the liver. After 2 h, 60% of injected ^{3}H-COEth was still liver-associated, and no radioactivity could be detected in serum, bile or intestinal mucosa. Apparently, no direct uptake or translocation of TG-rich lipoproteins took place. At 2 h after injection of ^{3}H-CO-particles, considerable ^{3}H-CH could be detected in serum, bile, and intestinal perfusate. Serum lipid profiling showed that the distribution of ^{3}H in ^{3}H-CO treated mice was similar to that of total CH, and was mainly found in HDL. Interestingly, specific CH activity in perfusate was 4-fold higher than that found in the mucosa of the perfused intestine suggesting highly specific trafficking of CH from serum lipoproteins across the enterocyte. In conclusion, these data support the presence of an intestinal cholesterol secretion path-way and show that TG-rich lipoproteins do not contribute to this pathway directly.

Enhanced biliary cholesterol secretion in Atp8b1 mutant mice is Abcg5/8 independent

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Progressive Familial Intrahepatic Cholestasis type 1 (PFIC1) is an autosomal recessive disease, characterized by severe intrahepatic cholestasis. PFIC1 is caused by mutations in ATP8B1 encoding a putative phosphatidylserine flippase. The role of Atp8b1 can be studied in vivo, using a mutant mouse model with the most common mutation (G308V) which leads to near complete absence of the protein. *Atp8b1*$^{G308V/G308V}$ mice have a strongly increased biliary output of PS and canalicular ecto-enzymes upon taurocholate (TC) infusion. In addition, *Atp8b1*$^{G308V/G308V}$ mice secrete about twice the amount of cholesterol in bile upon taurocholate infusion compared to wild types. These data suggest that the absence of Atp8b1 leads to a reduced bile salt resistance of the canalicular membrane with enhance extraction of lipids and ecto-enzymes as a consequence.
The aim of this study was to test the mechanism of enhanced biliary cholesterol excretion in *Atp8b1*$^{G308V/G308V}$ mice.
Atp8b1$^{G308V/G308V}$ mice were backcrossed to C57Bl/6 background and crossed with the *Abcg8*$^{-/-}$ mice to generate *Abcg8*$^{-/-}$*Atp8b1*$^{G308V/G308V}$ mice (GF mice). In these animals we analyzed biliary excretion upon infusion of increasing amounts of TC (400-1600 nmol/min.100gr body wt). We also analyzed Abcg5/g8 expression in wild type and *Atp8b1*$^{G308V/G308V}$ mice under control conditions and after treatment with Lxr agonist (TO-901317).
As reported before biliary excretion of cholesterol was significantly reduced in *Abcg8*$^{-/-}$ mice (both under control conditions and during TC infusion). In *Atp8b1*$^{G308V/G308V}$ biliary cholesterol excretion was 2-fold increased as compared to syngeneic wild type mice. Biliary cholesterol excretion in GF mice was as high as in *Atp8b1*$^{G308V/G308V}$ irrespective of the fact that Abcg8 was completely absent. *Atp8b1*$^{G308V/G308V}$ and wild type mice were equally responsive to the Lxr agonist in terms of induction of Abcg5 and Abcg8 expression and absolute increase in biliary cholesterol excretion.
In mice lacking Atp8b1, Abcg5/8 expression and function are normal. However, in Atp8b1 deficient mice there is a doubling of biliary cholesterol excretion and the increased cholesterol output is completely independent of Abcg5/8. These data support our hypothesis that Atp8b1 deficiency leads to a reduced resistance of the canalicular membrane towards hydrophobic bile salts with enhanced cholesterol as a consequence.

ABCB11 activity is regulated by the cholesterol content of the canalicular membrane

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Progressive familial intrahepatic cholestasis type 1 (PFIC1) is caused by mutations in *ATP8B1*. This transporter is thought to be a flippase for phosphatidylserine (PS) but the mechanism whereby impaired ATP8B1 function results in cholestasis is unclear.
AIM of this study was to elucidate the mechanism of cholestasis in PFIC1 using *Atp8b1*$^{G308V/G308V}$ mice. These mice have only very mild cholestasis, but accumulate very high amounts of bile salts in serum upon cholate feeding.
METHODS *Atp8b1*$^{G308V/G308V}$ were infused with increasing amounts of taurocholate (TC, 0-1600 nmol/min.100g body weight) and biliary excretion was analyzed. Abcb11 expression, localization and activity were analyzed in tissue and membrane preparations from wild-type and *Atp8b1*$^{G308V/G308V}$ mice.
RESULTS Upon TC infusion, biliary excretion was increased for phosphatidylcholine (10%), cholesterol (100%), and alkaline phosphatase (600%) in *Atp8b1*$^{G308V/G308V}$ mice compared to wild-type mice. Phospholipid analysis revealed that PS was absent from wild-type bile whereas significant amounts of PS (4% of total PL) could be detected in bile from *Atp8b1*$^{G308V/G308V}$ mice. During infusion, hepatic TC levels were 2.5-fold higher in *Atp8b1*$^{G308V/G308V}$ compared to wild-type mice, indicative of a mild cholestasis in the mutant animals. We hypothesized that increased phospholipid randomization in the canalicular membrane of *Atp8b1*$^{G308V/G308V}$ mice leads to enhanced extraction of cholesterol. The latter event may cause dysfunction of ABCB11. ATP-dependent TC transport was measured in liver membranes that were depleted from cholesterol by incubation with increasing amounts of cyclodextrin (CD). We observed a near linear relation between ABCB11 activity and membrane cholesterol content. When 80% of membrane cholesterol was depleted, the ATP-dependent bile salt transport activity was completely abrogated. This effect was reversible as cholesterol repletion to these membranes completely restored the bile salt transport activity.
CONCLUSION: ABCB11 transport activity is critically dependent on the membrane cholesterol content. We hypothesize that the disproportionate extraction of cholesterol from the canalicular membrane in *Atp8b1*$^{G308V/G308V}$ mice leads to reduced Abcb11 activity and cholestasis.

Interaction of ATP8B1 with CDC50A/B is required for endoplasmic reticulum exit and plasma membrane flippase activity

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ATP8B1 is a type 4 P-type ATPase and a putative lipid flippase that translocates lipids from the exoplasmic- to the cytoplasmic leaflet of bilayers. Mutations in *ATP8B1* cause progressive familial intrahepatic cholestasis type 1 (PFIC1), a severe liver disease characterized by a chronic intrahepatic cholestasis which progresses to end-stage liver disease. We have previously shown in mice that Atp8b1 is essential for maintaining the detergent-resistant properties of the canalicular membrane. Atp8b1-deficient mice displayed elevated biliary concentrations of cholesterol and phosphatidylserine. These findings implicate that Atp8b1 translocates phosphatidylserine.
Aim of this study was to elucidate the molecular mechanisms of ATP8B1-dependent translocation of lipids.
Methods: We have isolated 2 cDNAs encoding human CDC50A and CDC50B, homologs of yeast accessory proteins, involved in proper trafficking of yeast type 4 P-type ATPases. Using lentiviral transduction, we have generated non-polarized Chinese hamster ovary (CHO) cell lines expressing ATP8B1 or green fluorescent protein (GFP)-tagged ATP8B1 (ATP8B1-GFP), and cell lines co-expressing ATP8B1(-GFP) and CDC50A or CDC50B. In these cell lines we have studied trafficking and localization of the proteins by immunofluorescence microscopy and co-immunoprecipitation. We have studied the translocation of fluorescently (NBD)-labeled phosphatidylserine (NBD-PS) after incubation for 15 minutes at 15 degrees celcius and quantification of intracellular fluorescence.
Results: When expressed alone, both ATP8B1-GFP and CDC50A or CDC50B localized predominantly to the endoplasmic reticulum. In line with this observation, we detected only little ATP8B1-dependent NBD-PS translocation (20% increase compared to control). However, co-expression of ATP8B1-GFP and CDC50A or CDC50B retargeted both proteins from the endoplasmic reticulum to the plasma membrane. Co-immunoprecipitation demonstrated that ATP8B1(-GFP) physically interacts with both CDC50A and CDC50B. Co-expression of ATP8B1 and CDC50B resulted in a 70% increase in NBD-PS translocation compared to control, whereas CDC50A did not stimulate ATP8B1-dependent NBD-PS translocation.
Our data implicate that CDC50 proteins are possible ß-subunits of ATP8B1 and are pivotal factors in correct trafficking of ATP8B1. It is possible that they are also essential for activity of the protein. Consequently, CDC50 proteins may be novel and essential determinants of ATP8B1-related disease.

Functional donor dendritic cells migrate after liver transplantation via the bloodstream into the recipient

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It is generally thought that after organ transplantation donor dendritic cells (DC) migrate from the graft into the recipient and induce anti-donor T-cell reactivity leading to graft rejection. However recent experimental animal studies suggest that donor graft-derived DC can also promote tolerance to the graft instead of rejection. Though both migration and functional properties of liver graft DC have never been investigated in clinical transplantation.We determined by flowcytometry whether donor DC and for comparison donor B-cells were present in the circulation of liver graft recipients (n=10) during the early post-transplantation period. DC were defined as BDCA1+CD20-cells and their origin was determined using HLA-A2 mismatches between donor and recipient. To study the functional properties of liver graft DC, we purified DC that detached from liver grafts during pre-transplant perfusion (n=6), and compared them to blood DC (n=7).In 9 out of 10 liver graft recipients donor DC were detected in the circulation on day 1 after liver transplantation, and made up 4.6% (range 0-18%) of total circulating DC. This fraction was higher in comparison to circulating B-cells, of which only 1.5% (range 0.3-5.7%) were donor-derived (p=0.046). On day 5 after liver transplantation donor DC (0.81%; range 0.20-1.32%) and donor B-cells (0.50%; range 0.35-0.48%) were still present in the blood of the recipients. Liver graft DC were immature DC with a low expression of CD86, CD83, and CCR7, which was comparable to blood DC (p> 0.14). Upon stimulation with LPS, liver graft DC produced significantly more IL-10 than blood DC (1995±1724 versus 137±45 pg/ml; p= 0.003). Both types of DC did not produce IL-12.
Conclusion. After liver transplantation donor-derived DC migrate from the donor liver via the bloodstream into the recipient. These DC have a high capacity to produce the immunoregulatory cytokine IL-10 and may contribute to the relatively low incidence of rejection after liver transplantation in comparison with other solid organ transplantations.

TNF-α partially abrogates regulatory T cell mediated suppression of the anti-HBV immune response in patients with a chronic infection.

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Chronicity of hepatitis B virus (HBV) infection is characterized by a weak immune response to the virus. The proportion of CD4+CD25+*FoxP3*+ regulatory T cells (Treg) in peripheral blood of patients with a chronic HBV infection was increased compared to both healthy controls and to those who have resolved their HBV infection. These Treg were capable of inhibiting the T cell response against HBV core antigen (HBcAg). The mechanism by which Treg exert their suppressive effect remains unclear. Immuno regulatory cytokines such as interleukin (IL)10 and transforming growth factor (TGF)-β may play a role. The aim of our study was to determine the endogenous and exogenous factors involved in the HBV specific suppression by Treg.
Treg and Treg-depleted cell fractions were isolated from peripheral blood of patients with a chronic HBV infection using MACS beads. The *FoxP3* expression of isolated CD4+CD25+ cells and CD4+CD25- cells was determined by flowcytometry. Treg-depleted cells and Treg-depleted cells reconstituted with 20% Treg were stimulated with HBcAg. TNF-α (25 ng/ml), IL-1β (50 ng/ml), neutralizing antibodies against IL10 or TGF-β or isotype matched control antibodies were added to the HBcAg stimulated cells. After 6 days the proliferation was determined by ^{3}[H]-thymidine incorporation. The percentage of suppression was calculated using the following formula: (1- stimulation index with 20% Treg/ stimulation index Treg depleted cells) x 100%. All percentages are expressed as mean ± SEM.
FoxP3 was expressed by 68% of the isolated CD4+CD25+ cells and by 7% of the isolated CD4+CD25- cells. The Treg were capable of inhibiting the response against HBcAg and tetanus toxin (n=17), however the suppressive effect on the proliferation against HBcAg was stronger (60% ± 5 (HBcAg) vs. 27% ± 12 (tetanus toxin)).This suppressive effect of the response against HBcAg was partially abrogated by TNF-α (61% suppression ± 6 (no cytokine) vs. 27% ± 8 (TNF-α), p = 0.027). IL-1β had no effect on Treg mediated suppression (54% ± 9) (n=9). Neutralization of IL10 and TGF-β had no effect on Treg mediated suppression (n=5).
In conclusion, suppression of the HBV specific immune response by Treg can be abrogated by adding TNF-α. The suppression by Treg is not mediated through production of IL10 and TGF-β. This implies that TNF-α could be an important mediator of the perpetuating chronic HBV infection.

Increased risk of hepatocellular carcinoma among patients with hepatitis C cirrhosis and diabetes mellitus

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Summary: For patients with hepatitis C cirrhosis the risk for development of hepatocellular carcinoma is about 2-10% per year. Recent studies suggest that the presence of diabetes mellitus increases the risk of developing hepatocellular carcinoma. The aim of this study is to quantify the risk of hepatocellular carcinoma among patients with both diabetes mellitus and chronic hepatitis C in a large cohort of patients with advanced fibrosis. We included 541 patients of whom 85 (16%) had diabetes mellitus. The mean age at inclusion was 49 years. There were no differences in body mass index between patients with or without diabetes mellitus (27 vs 26 kg/m^2, NS). The prevalence of diabetes mellitus was 10.5% among patients with an Ishak fibrosis score of 4, 12.5% for Ishak 5 and 19.1% for Ishak 6. Multiple regression analysis showed that only cirrhosis (Ishak score 6) was independently associated with diabetes mellitus (p=0.028). During a mean follow-up of 3.3 years, 11 patients (13%) with diabetes mellitus developed hepatocellular carcinoma versus 27 patients (5.9%) without diabetes mellitus. The 5-year occurrence of hepatocellular carcinoma was 18.6% (6.8-30.4) and 5.3% (2.3-8.3) for patients with and without diabetes mellitus (p=0.026). Multivariate Cox regression analysis of patients with Ishak 6 cirrhosis showed that diabetes mellitus was independently associated with the development of hepatocellular carcinoma. Conclusion: The 5-year occurrence of hepatocellular carcinoma is 18.6% among patients with hepatitis C advanced fibrosis and diabetes mellitus. This is three times as high as in a comparable population without diabetes mellitus.

Mycophenolic Acid Inhibits Hepatitis C Virus Replication Independent Of Guanosine Depletion And Acts In Synergy With Interferon-α

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Body: Chronic hepatitis C virus (HCV) infection is the leading indication for liver transplantation worldwide. Mycophenolic acid (MPA) is a highly effective immunosuppressant through the inhibition of T cell proliferation. MPA has anti-viral properties against several viruses, including HBV, HIV and West Nile virus, but no clear effect has been reported for HCV. The anti-proliferation and the anti-viral activity has attributed to the ability of MPA to inhibit de novo guanosine nucleotide production. Accordingly, supplementation of guanosine can overcome the viral inhibition by MPA. In this study we investigate the effect of MPA on HCV replication in vitro and explore the anti-viral mechanism of action. Recent findings have directed the mechanism search to the HCV NS5b RNA dependent RNA polymerase.
Methods: The anti-viral properties of MPA and pegylated IFN-alpha 2b (IFN) were tested in vitro using an HCV-replication model. Huh-7 hepatoma cells, containing the HCV replicon with a luciferase reporter gene, were cultured for 18 hours with different doses or combinations in the presence or absence of exogenous guanosine. HCV replication was quantified based on luciferase activity, RT-PCR for viral RNA and immunocytochemistry for helicase (NS3) protein.
Results: At clinically relevant concentrations (1.0-6.0 µg/ml), MPA inhibited HCV replication to approximately 75%. Similar reduction was observed on the level of HCV viral RNA and NS3 protein expression. In these short-term experiments, MPA did not inhibit replicon cell proliferation or induce cell death, which could have accounted for the anti-viral effect. The addition of exogenous guanosine did little to reverse the anti-viral activity of MPA on HCV replication, though completely reversed the inhibition of West Nile Virus replication. When combined with suboptimal concentrations of IFN, MPA showed significant synergistic inhibition of replication.
Conclusion: The immunosuppressive drug MPA is a potent inhibitor of HCV replication. MPA was shown to have a distinct anti-HCV mechanism of action, independent of cell proliferation and guanosine depletion. These results suggest that MPA could reduce HCV recurrence after liver transplantation and could act as an adjuvant to IFN-α anti-viral therapy.

Randomized placebo controlled phase I/II trial of a-galactosylceramide (KRN7000) for the treatment of chronic hepatitis C

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For chronic hepatitis C patients not responding to treatment with peginterferon and ribavirin, new treatment options should be explored. The glycosphingolipid α-galactosylceramide (KRN7000) has been shown to activate invariant natural killer T cells when presented in the context of CD1d and induces powerful antiviral immune responses via the production of inflammatory cytokines, including interferons and tumour necrosis factor-α.

The aim of this international multicenter randomized placebo-controlled trial was to investigate the safety and the antiviral activity of α-galactosylceramide as a novel class of treatment for chronic hepatitis C patients.

Fourty patients were enrolled into the study and allocated to either a dose of 0.1 μg/kg (n=9), 1 μg/kg (n=9), 10 μg/kg (n=11) or to placebo (n=11).

α-Galactosylceramide was well tolerated and no patients were withdrawn because of side effects. Although most patients showed a decrease in invariant natural killer T cells after administration, no clinically relevant suppression of viral replication was observed during α-galactosylceramide therapy. Only one patient, a previous non-responder to peginterferon and ribavirin who had high baseline invariant natural killer T cell levels, showed profound signs of immune activation. This patient had a transient 95% decrease in HCV RNA levels and a concomitant increase in ALT levels after the first administration.

In conclusion, α-galactosylceramide used as monotherapy for interferon-refractory patients in doses of 0.1 to 10 μg/kg is safe, however in its current form it exerts limited effectiveness in suppressing hepatitis C viral replication.

Nasobiliary drainage induces complete and long-lasting remission in benign recurrent intrahepatic cholestasis*

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Benign recurrent intrahepatic cholestasis (BRIC) is characterized by attacks of cholestasis without anatomical obstruction. Although these episodes do not result in permanent liver damage, the resulting pruritus is severely disabling. Consistently effective medical treatment is not available. In BRIC type 1, caused by mutations in ATP8B1, cholestasis may be associated with enhanced re-uptake of bile salts. We hypothesized that a temporary interruption of the enterohepatic circulation could abort a cholestatic episode in these patients. At present, bile diversion has been established by endoscopically introducing a nasobiliary drain during eleven cholestatic episodes in nine patients with BRIC type 1. In 9/11 treatments, pruritus totally disappeared within 48 hours and serum bile acid levels returned to normal or near normal levels. After removal of the drain generally a short biochemical relapse was experienced, which required no further intervention. No serious complications were observed. During diversion, in three patients bile was collected for one hour to analyze its composition. Relative amounts of biliary phospholipids versus bile salts were within the normal range. Further analysis of phospholipid classes revealed decreased proportions of phosphatidylcholine and increased proportions of other phospholipids such as phosphatidylethanolamine and phosphatidylserine. This may reflect a compromised function of FIC1, which is proposed to be an aminophospholipid flippase.
In conclusion we have shown that temporary NBD induces complete and long lasting remission of cholestasis in BRIC1 patients and we propose that this therapy should be considered in cholestatic BRIC patients. In addition, in BRIC type 1 patients no evidence for primary disorder in the hepatic transport of bile acids could be found by direct analysis of bile obtained at diversion.

ALT flares occur often after delivery in patients with chronic hepatitis B virus infection

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During pregnancy there are alterations in the immune status to allow mothers to tolerate the genetically different fetal tissues. One of these changes is a shift of the maternal immune system towards a T-helper 2 immunity. We investigated the evolution of the liver disease during and after pregnancy in chronic hepatitis B patients. Between 1998 and 2006 there were 38 pregnancies in 31 women. Eighteen patients (58%) were HBeAg-positive, 13 (42%) HBeAg-negative. Nine patients (29%) had been treated before pregnancy of which 7 patients received lamivudine treatment. Twenty-four subjects (63%) were immunotolerant, 4 (11%) immune-active and 10 (26%) subjects were in the immune-control phase before pregnancy. The mean age at the time of delivery was 26.7 years (range, 18.2-40.5). In 13 pregnancies (34%), lamivudine therapy was started in the last trimester of pregnancy to lower HBV DNA levels and thereby reducing the risk of vertical transmission; lamivudine was stopped directly after delivery in all those pregnancies. A post pregnancy flare was defined as a 3 times increase in ALT within 6 months after delivery compared to the lowest ALT value during pregnancy. Seventeen of these flares occurred in the 38 pregnancies (45%) at a mean of 61 (range, 5-129) days after delivery. Even in the absence of lamivudine treatment during the last trimester of pregnancy, post pregnancy flares occurred in 36% (9/25) of the pregnancies. In patients with lamivudine treatment this percentage was 62% (8/13) (p=.13). Mean ALT declined from 1.0 times the upper limit of normal (x ULN) before to 0.7 x ULN during pregnancy. For those with a post pregnancy flare, mean peak ALT level raised to 4.3 x ULN. Without a post pregnancy flare, ALT returned to 1.0 x ULN. There was no marked influence of lamivudine use during pregnancy on the severity of flares.HBV DNA levels before and during pregnancy tended to be higher in patients with a post pregnancy flare (7.2 and 7.4 log copies/ml, respectively) compared to those without (5.9 and 6.5 log copies/ml, respectively) (p=.25 and .28). Furthermore, HBeAg-status did not influence the occurrence of post pregnancy flares (p=.86).
In conclusion, ALT flares occur often after pregnancy, even in the absence of lamivudine treatment. These flares may be due to a reactivation of the immune system after delivery. Based on our data we recommend to monitor for HBV related flares and if necessary treat women with chronic HBV in the months after delivery.

Efficacy and prediction of response in a single center cohort of chronic hepatitis B patients treated with adefovir dipivoxil

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Adefovir is effective for wild type and lamivudine refractory chronic hepatitis B. Treatment outcomes, response prediction and feasibility of stopping rules in case of non-response to therapy were studied in patients treated with adefovir dipivoxil for at least 48 weeks in a single center university hospital. Sixty-nine chronic hepatitis B patients were treated with adefovir monotherapy 10 mg once daily. From 60 patients data at week 48 were available. At baseline HBeAg was positive in 45%, 28% had never received antiviral therapy before, 58% received prior lamivudine treatment and 36% of patients had a documented history of lamivudine resistance. Median viral decline was 2.51 $\log_{10}$ copies/ml after 48 weeks. HBV DNA was undetectable (<400 copies/ml) in 10%, 37% had a viral load below 10^3 copies/ml and ALT normalised in 62%. HBeAg-seroconversion occurred in 24% of e-positive subjects. Mutations were found in 3/41 sequenced samples with HBV DNA >10^3 copies/ml. Patients with a baseline viral load >10^5 copies/ml had a 3.56 $\log_{10}$ copies/ml decline, PCR negativity in 2%, <10^3 copies/ml in 30% and ALT normalisation in 62%. Treatment outcomes defined did not differ between patients with or without lamivudine resistance. Viral decline 2.41 vs. 2.63 $\log_{10}$ copies/ml; p=0.59.
Baseline HBV DNA was higher in e-positive compared to e-negative subjects (8.54 vs. 6.36 $\log_{10}$ copies/ml, p<0.0001). Viral decline was similar (2.71 vs 2.40 $\log_{10}$ copies/ml; p=0.68) and PCR negativity was reached in 4% vs. 16%; p=0.13.
Stopping rules based on actual viral load thresholds of 10^4 copies/ml at 12 and 24 weeks were very accurate to predict non-response (≥10^3 copies/ml at week 48, chance of response <5%). At week 12 and 24 the Negative Predictive Value (NPV) was 96%. At week 12 the specificity (proportion of non-responders identified by the stopping rule) was 71% and the sensitivity 95%. At week 24 the specificity was 68% and the sensitivity of 95%. The accuracy of the definition of primary non-response (<1 $\log_{10}$ IU/ml decline after 12 weeks) to predict non-response in patients with a baseline load >10^5 copies/ml, was clinically confirmed. The NPV was 100%, specificity 18% and sensitivity 100%.
In conclusion, adefovir monotherapy evaluated in a single center cohort is a potent drug but viral response appears to be less compared to large registration trials. Virologic non-response at 48 weeks could be predicted with great accuracy by HBV DNA assessment after 12 weeks of treatment.

The impact of intraoperative findings on the surgical treatment strategy of patients with colorectal liver metastases

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Imaging techniques play a crucial role in the assessment of patients with colorectal liver metastases (CRLM). Intraoperative ultrasonography (IOUS) is considered the gold standard to accurately identify and localize hepatic metastatic lesions. Computed tomography (CT) scans are used preoperatively to map the CRLM and determine resectability. However, the accuracy of modern helical CT scanning is largely undetermined. Also, it is uncertain to what extent discrepancies between preoperative imaging and intraoperative findings (IOUS + surgical exploration) affect surgical decision-making and treatment strategy. The aim of this study is to evaluate the accuracy of preoperative CT scanning compared to intraoperative findings in patients treated for CRLM and whether discrepancies changed treatment strategy in our patient population.All patients who underwent a laparotomy because of CRLM between January 2000 and March 2006 were included. All patients had preoperative helical CT scanning followed by IUOS of the liver. Also, surgical exploration was conducted to assess evidence of local disease and/or peritoneal metastases. IOUS plus surgical exploration was compared to CT and surgical reports were analyzed to detect changes in treatment strategy. In this 6-year period, 100 patients with CRLM had a laparotomy 117 times with the intent of surgical treatment. IOUS alone had different findings in 26% compared to the preoperative CT scan, more lesions in 16% (mean 1.5 (1-4)), additional information on localization in 9%. IOUS and surgical exploration combined changed the surgical treatment strategy in 37%. In only 3 patients, new information did not alter the surgical treatment. Preoperative CT failed to predict peritoneal metastases in 4 patients (carcinomatosis in 2 patients) and diffuse hepatic metastases in 3 patients. Also, in 7 patients surgical exploration found evidence of local extension of the CRLM (diaphragmatic invasion in 5 patients, anterior abdominal wall invasion in 2 patients), not seen on CT.
Conclusions: IOUS ± surgical exploration provided new or additional information regarding number, localization and/or local extension of the CRLM in 39% of cases. Discrepancies between preoperative imaging and intraoperative findings changed the surgical treatment strategy in most (93%) of these cases. The combination of IOUS and surgical exploration is an essential diagnostic tool in the assessment of patients with CRLM undergoing surgical treatment.

The progression of premalignant gastric lesions to gastric cancer in the Netherlands

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Gastric cancer is the fourth most common cancer and second leading cause of cancer related death worldwide. Although the incidence of gastric cancer in the Netherlands has declined over the past decades, still nearly 2000 cases are diagnosed each year. Gastric cancer of the intestinal type is commonly preceded by premalignant lesions, i.e. gastric atrophy, intestinal metaplasia and dysplasia. Therefore, surveillance of patients with premalignant lesions could mean a basis for gastric cancer prevention. The aim of this study was to evaluate the histological incidence and surveillance of patients with premalignant gastric lesions in the Netherlands. A cohort-study was performed through analysis of data obtained from the Dutch nationwide pathology database (PALGA). Data from patients with a first diagnosis of a premalignant gastric lesion between 1991 and 2005 were evaluated. Patients with a history of esophageal or gastric resection or cancer prior to the first diagnosis of a premalignant lesion were excluded. Patients with a previous or simultaneous diagnosis of Barrett's esophagus were excluded from evaluation of surveillance. 100.130 patients received a new diagnosis of a premalignant gastric lesion during the investigated period. The mean annual incidence of new diagnoses was 1595 for gastric atrophy, 4475 for intestinal metaplasia and 610 for dysplasia. After a diagnosis of gastric atrophy or intestinal metaplasia respectively 25 and 27 percent of patients received a re-evaluation gastroscopy, compared to 40 percent after a diagnosis of dysplasia. Surveillance, defined as 3 or more gastroscopies after initial diagnosis, was performed in 2% of patients with gastric atrophy or intestinal metaplasia, and in 6% of patients with dysplasia. Patients who underwent subsequent gastroscopies were significantly younger than patients who did not ($p<0.001$). Conclusions: Premalignant gastric lesions are commonly encountered during gastroscopy. In clinical practice, surveillance of these lesions is in the vast majority of patients omitted, even when overt dysplasia is diagnosed. The necessity of surveillance of premalignant gastric lesions requires further investigation.

The progression of premalignant gastric lesions to gastric cancer in the Netherlands

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Gastric cancer of the intestinal type is commonly preceded by premalignant stadia, i.e. gastric atrophy, intestinal metaplasia and dysplasia. Surveillance of patients with premalignant lesions could mean a basis for prevention of gastric cancer. However, international guidelines for surveillance are lacking and its benefit is unclear, among others because the incidence of gastric cancer in patients with these preneoplastic conditions is unknown. The aim of this study was to evaluate the progression of premalignant gastric lesions to gastric cancer in the Netherlands.A cohort-study was performed through analysis of data obtained from the Dutch nationwide pathology PALGA database. Data from all patients with a first diagnosis of a premalignant gastric lesion between 1985 and July 2005 were evaluated. Patients with a history of esophageal or gastric resection or cancer prior to the first diagnosis of a premalignant lesion were excluded from analysis. A cohort of 120.012 patients with a new diagnosis of a premalignant gastric lesion during the investigated period was identified, with a male: female ratio of 1.1:1 and a median age of 65 years. The mean investigated period was 9 years. Within this cohort 2.285 patients (0.9%) developed distal gastric cancer during the investigated period at a median age of 73 years. From the subgroup of 29.387 patients with atrophic gastritis 254 (0.9%) patients developed gastric cancer, compared to 1.339 of 78.386 (1.7%) patients with intestinal metaplasia and 692 (5.7%) of 12.239 patients with dysplasia. The mean period between the premalignant diagnosis and gastric cancer was 3.8 years for patients with atrophic gastritis, 3.4 years for intestinal metaplasia, 3.4 years for mild dysplasia, 2.7 years for moderated dysplasia and 0.8 years for severe dysplasia.
Conclusions: The risk of gastric cancer after the diagnosis of premalignant gastric lesions is substantial. Therefore, development of national surveillance guidelines should be considered.

Validation of the O-POSSUM-score in patients with oesophageal cancer

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To reliably compare the operative results of different institutes, it is of pivotal importance that the used model discriminates patients with a higher risk from those with a lower risk for in-hospital mortality. “The Physiological and Operative Severity Score for the enUmeration of Mortality adjusted for oesophagogastric surgery”(O-POSSUM) has been developed to predict in-hospital mortality in these patients taking into account operative risk factors, and thus the so-called case-mix1. However, O-POSSUM has never been validated. Therefore, the aim of the present study was to externally validate O-POSSUM. Data on patients who underwent potentially curative oesophagectomy in a tertiary referral centre for adenocarcinoma or squamous cell carcinoma of the oesophagus were analyzed. Mortality predicted by O-POSSUM was compared to the actual mortality with the method of linear analysis. Receiver Operator Characteristic curve analysis was used to analyse if the model could discriminate patients who die from those who survive. The Hosmer and Lemeshow goodness of fit test was used to analyse if observation of in-hospital mortality fitted prediction when stratified for the various operative risk factors. Between January 1993 and August 2005 a total of 677 patients underwent oesophagectomy for carcinoma. A total of 25 patients (3.7%) died in the hospital due to postoperative complications. O-POSSUM predicted in-hospital mortality in 84 patients (12.4%). The area under the Receiver Operator Characteristic curve was 0.61 (95% confidence interval 0.49 to 0.74, p=0.053). The O:P (observed: predicted) ratio for in-hospital mortality was 0.30 and the model had a significant lack of fit (p<0.001) using “goodness-of-fit” analysis.
Conclusion: In patients who underwent oesophagectomy for cancer of the oesophagus in a tertiary referral centre, O-POSSUM overpredicted in-hospital mortality threefold. More importantly, O-POSSUM could not identify patients with a higher risk for in-hospital mortality. Therefore, the O-POSSUM score needs substantial modification before it can be applied for the comparison of treatment outcomes between different institutes which perform oesophageal cancer surgery. 1 P.P. Tekkis, P. McCulloch, J.D. Poloniecki et al. Risk-adjusted prediction of operative mortality in oesophagogastric surgery with O-POSSUM.

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Metformin protects hepatocytes against oxidative stress induced apoptosis via HO-1 induction and inhibition of JNK activation.

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Background: The majority of chronic liver diseases are accompanied by oxidative stress, which may induce apoptosis in hepatocytes and liver injury. Oxidative stress is also involved in the pathophysiology of diabetes complications. Metformin, an insulin sensitizing agent, has been shown to be hepatoprotective in the insulin-resistant and leptin deficient ob/ob mouse model of NAFLD. Previously, we reported that metformin protects hepatocytes against oxidative stress induced apoptosis. However, the mechanism involved in this protective effect has not been elucidated yet. Aim: To elucidate the mechanism involved in the protective effect of metformin against oxidative stress-induced apoptosis.
Methods: Primary hepatocytes were exposed to the superoxide anion donor menadione (50µM) with and without different doses of metformin, added 30 min before menadione treatment. In some experiments, hepatocytes were infected with an adenovirus overexpressing HO-1 or with a control adenovirus before menadione exposure. HO-1 mRNA expression was determined by Q-PCR. Apoptosis was determined by measuring caspase-3 and -6 activity and PARP cleavage, and necrosis was measured by Sytox Green nuclear staining. Results: 1) Metformin inhibits menadione-induced PARP-cleavage and apoptosis dose dependently (50% inhibition at 0,1mM metformin; >90% inhibition at 0,5 and 1mM metformin). 2) Menadione induced HO-1 mRNA expression up to 20-fold of control. Co-treatment with metformin dose-dependently further induced HO-1-expression up to 100-fold of control, whereas metformin alone did not change HO-1-expression compared to control. 3) HO-1 overexpression, using an adenoviral construct, before menadione treatment inhibits menadione-induced apoptosis. 4) Menadione-induced apoptosis is dependent on JNK pro-apoptotic activity, since the JNK-inhibitor SP600125 abolishes menadione-induced apoptosis. 5) Menadione induces JNK-phosphorylation but co-treatment with metformin reduces JNK-phosphorylation.
Conclusions: Metformin protects hepatocytes against superoxide anions-induced caspase activation, PARP cleavage and apoptosis. The anti-apoptotic effect of metformin is in part dependent on the induction of HO-1 expression and inhibition of JNK-activation. Metformin-induced JNK inhibition could explain its beneficial effect in diabetes, since JNK interferes with insulin signalling. Our results elucidate a completely novel protective mechanism of metformin, which could represent an attractive target

Gastrojejunostomy versus stent placement in patients with malignant gastric outlet obstruction: a comparison in 95 patients

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Gastric outlet obstruction (GOO) is frequently seen in patients with malignancies of the upper gastrointestinal tract, i.e. distal stomach, periampullary and duodenal carcinoma. Gastrojejunostomy (GJ) is the most commonly performed palliative treatment for GOO and is associated with good functional outcome on the long term. However, patients having undergone a GJ often experience significant morbidity and even mortality. Recently, stent placement has been introduced, which may have better short term outcomes. In this retrospective study, we compared GJ and stent placement, with respect to technical and clinical success, complications, hospital stay and survival. Fifty-three patients were referred for stent placement and 42 patients underwent GJ in the period 1994 to 2006. No differences in technical success rates (93% (stent) vs. 100% (GJ); p=0.5) were found. Clinical success, defined as relief of symptoms and improvement of food intake to at least soft solids, was not different between stent placement and GJ (81% vs. 60%; p=0.14). The GOOSS score (Gastric Outlet Obstruction Scoring System) after treatment (scale 0 (no oral intake) - 3 (full diet)) was similar for stent placement and GJ (1.94 vs. 1.85; p=0.6). Early (<7 days) major complications (i.e., stent migration, severe bleeding and perforation), occurred more frequently after GJ (17% vs. 4 %; p<0.05), whereas minor complications (i.e., mild pain vomiting, wound infection (GJ)) occurred more frequently after stent placement (43% vs. 12%; p<0.001). Hospital stay was shorter after stent placement than after GJ (mean 6 vs. 18 days; p<0.001). No differences in occurrence of late (> 7 days) major complications (28% (stent) vs. 19% (GJ); p=0.15) and survival (100 (stent) vs. 129 days (GJ); p=0.2) were seen.
Conclusion: Both GJ and stent placement are safe and effective treatment modalities for the palliation of GOO. The presently ongoing randomized trial, the SUSTENT study, will likely answer the question which treatment is most optimal for patients with GOO, with regard to medical effects, quality of life and costs/cost-effectiveness.

The GI Mentor II simulator: validation and learning curves

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The main objectives of this study were to establish the degree of representation of real-life colonoscopies on the Simbionix GI Mentor II VR simulator as judged by experts and to determine whether this simulator can distinguish between experienced endoscopists and novices performing VR colonoscopy.MethodsFour groups were selected to perform two colonoscopies and one hand-eye coordination task (EndoBubble level 1) on the GI Mentor II simulator. The 1th group, novices, were defined as participants without endoscopic experience. The 2nd group, intermediate experienced, defined by the number of colonoscopies performed, being less than 200. The 3rd group consisted of experienced endoscopists, defined as between 200 and 1000 colonoscopies performed. The 4th group, experts all had performed more than 1000 colonoscopies. Intermediate, experienced and expert endoscopists were tested during the spring meeting of the Dutch Society of Gastroenterology in 2006. All persons were asked to fill out a questionnaire about previous experience in endoscopy and appreciation of the reality of the colonoscopy simulations performed. Appreciation was expressed on various aspects on a 4 point scale varying from very unrealistic to very realistic. The average time to reach the coecum was defined as one of the main test-parameters as well as the number of times the view of the lumen was lost.ResultsThe group of expert endoscopists rated the colonoscopy simulation 2.79 for reality overall. Expert-opinion was that the GI Mentor II simulator should be included in the training of novices (3.51). Novices (N=31) reached the cecum in an average time of 30:13 (min:sec), intermediates (N=13) in 6:09, experienced (N=16) in 4:19 and experts (N=35) in 4:56. Novices lost the view of the lumen significantly more often compared to the other groups. The EndoBubble task was also completed significantly faster by increasing grade of experience. These differences are statistically significant using a Kruskal Wallis Test ($p<0.001$). A separate analysis of experienced versus experts demonstrated no significant difference in time to reach cecum.
Conclusion: In this study we have demonstrated that the GI Mentor II simulator does offer a convincing realistic representation of colonoscopy according to experts and that the simulator can discriminate between different levels of expertise in colonoscopy. According to experts the simulator can be integrated in the training program of novices

Acquiring colonoscopy skills on the gi mentor ii; the learing curve

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Introduction: Teaching novice endoscopists the fundamentals of colonoscopy outside the clinical setting is important to minimise discomfort for patients. The aim of this study is to assess the proficiency curve for basic colonoscopy skills using the Simbionix GI Mentor II Virtual Reality (VR) simulator by assessment of both core-skill and performance of VR colonoscopies.
Aims & methods: Twenty-three medical trainees with no prior flexible endoscopy experience performed four preset training sessions (one per day) within five consecutive days. Prior to the first session, participants filled out a questionnaire and received a familiarisation tour on the simulator. Each participant performed the core-skill hand-eye coordination task (EndoBubble level 1) once per session and 11 VR colonoscopy cases in total (two in first session, three in subsequent sessions) with the assignment to visualise the cecum as quick as possible, while causing as little discomfort or pain for the virtual patient as possible. Case 3 of colonoscopy module I was repeatedly performed at the end of each session.
Results: Mean age 23 participants: 25.8 years. Session 1: mean time to reach cecum in case I-3 of 00h29min30sec (00:08:03 - 01:28:19) with a mean of 2.43% (0% - 24%) time virtual patient was in pain, time to finish EndoBubble task 00:06:49 (00:02:54 - 00:20:25). Session 4: mean time to reach cecum in case I-3 of 00:07:31 (00:04:25 - 00:15:50) with a mean of 0% of time virtual patient was in pain, time to finish EndoBubble task 00:02:53 (00:01:33 - 00:05:17). Differences in scores between session 1 and 4 are statistically significant ($p<0.05$). Scores of noviceendoscopists for both session 1 and session 4 differ significantly from scores of both experienced endoscopists (200-1000 colonoscopies previously performed, N=15) and expert endoscopists (>1000 colonoscopies previously performed, N=35). Scores of novices for session 4 differ less from scores of both the experienced and experts, than scores of session 1.
Conclusion: In this study, we have demonstrated that novice endoscopists significantly improve their basic virtual colonoscopy skills by training in both core-skill hand-eye coordination tasks and VR colonoscopy on the Simbionix GI Mentor II simulator. The amount of training provided in this study was not sufficient for most participants to reach the plateau of the learning curve or the proficiency level of experienced endoscopists.

Stents are safe and effective for the palliation of malignant strictures near the upper esophageal sphincter

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Stents are a well accepted treatment modality for malignant esophageal disease. However, the use of stents in the cervical esophagus is limited due to patient intolerance caused by pain and globus sensation. The aim of this study was to determine the efficacy and safety of stent placement in patients with a malignant obstruction near the upper esophageal sphincter (UES).Between 1996 and 2005, 99 patients (mean age:66 yrs; male/female: 69/30) received a stent for a malignant stricture near the UES, due to tumor growth within 8 cm of the UES. Patients included had a primary esophageal carcinoma (n=65) or recurrent tumor after gastric tube interposition (n=34). Of these, 22 (22%) also had a fistula.The procedure was technically successful in 95/99 (96%) patients. Patients were treated with different types of stents; in 49 (49%) patients an Ultraflex stent was placed. Mean tumor length was 7.1 cm, however tumor length was longer in patients a with primary cancer compared to recurrent tumor (7.8 vs. 5.7 cm; p=0.002). The fistula was sealed in 18 (82%) patients. Forty three (43%) patients underwent prior radiation and/or chemotherapy. The mean distance between the incisors and the tumor was 20 ± 3 (range 12-24) cm, whereas the mean distance between the incisors and the upper margin of the stent was 18 ± 2 (range 12-23) cm. The dysphagia score improved in all patients from a median of 3 (liquids) to 1 (some difficulties with solids). Complications were seen in 30/99 (30%) patients. Major complications (aspiration pneumonia [8], hemorrhage [6], fistula [5] and perforation [3]) occurred in 20 (20%) patients, whereas, pain following stent placement was observed in 14 (14%) patients. Recurrent dysphagia occurred in 25 (25%) patients and was mainly caused by migration (n=4), tissue overgrowth (n=11) and food bolus compaction (n=6). Globus sensation was observed in 8 (8%) patients, however in none of the patients stent removal was indicated. Nine of 65 (14%) patients with primary cancer died within 30 days, compared to 12/34 (35%) patients with recurrent tumor (p=0.02). Median survival was 105 (primary cancer) and 64 (recurrent tumor) days, respectively (p=0.08).
Conclusions: Stent placement is safe and effective for the palliation of dysphagia and sealing of fistulas in patients with a malignant stricture near the UES. Based on these results, we recommend stent placement in this group of patients with a dismal prognosis.

Video autofluorescence imaging for dysplasia and cancer detection in patients with longstanding ulcerative colitis

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Patients with longstanding ulcerative colitis (UC) have an increased risk for the development of colorectal cancer. Therefore colonoscopic surveillance with random biopsies is currently recommended. However, endoscopic detection of dysplasia is difficult. Recently a new endoscopic imaging system, incorporating high resolution white light endoscopy (WLE) and autofluorescence imaging (AFI), has been developed. This system may improve the detection of dysplastic lesions. We designed a randomized cross-over study, in which we assess the feasibility and clinical value of the video-AFI system in surveillance colonoscopy for patients with longstanding UC.All consecutive UC patients, eligible for surveillance colonoscopy, are invited to participate in this study. During withdrawal, the colon is inspected twice in randomized order, once in the WLE mode and once with AFI. Targeted as well as random biopsies are taken. The histology of the biopsies is used as the gold standard.In this ongoing study, 37 patients have been included. Two patients had to be excluded because of insufficient colon preparation. In 35 patients (mean age 52 yrs), a total of 11 neoplastic lesions were found. Fourteen patients were assigned to start with AFI. A total of 27 lesions (2 dysplastic) were found with AFI in these patients. Subsequent WLE added 4 lesions (1 dysplastic). In 21 patients examined with WLE first, 32 lesions (3 dysplastic) were seen with WLE. Subsequent AFI yielded 17 additional lesions (0 dysplastic). A mean number of 41 (range 20-52) random biopsies were taken per patient, revealing dysplasia in 5 biopsies. The sensitivity of AFI for the detection of dysplasia was 25%; the positive predictive value 4.5%. The sensitivity and positive predictive value of WLE were 44% and 11% respectively.
Conclusion: The use of the video-AFI system is feasible, provided that the colon is properly prepared. These preliminary results suggest that the diagnostic yields of WLE and AFI for the detection of dysplasia are similar. Both techniques failed to detect the majority of dysplastic lesions.

Inter-observer agreement amongst non-expert endoscopists of narrow band imaging of early neoplasia in Barrett's esophagus.

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Mucosal and vascular patterns (e.g. mucosal morphology) can be used to differentiate non-dysplastic Barrett's esophagus (BE) from high-grade dysplasia (HGD) or early cancer (EC). We have recently investigated the mucosal morphology of HGD/EC and non-dysplastic BE using narrow band imaging (NBI) and proposed a 3-step classification for the evaluation of BE: determination of the regularity of the mucosal pattern, the regularity of the vascular pattern and the presence of abnormal blood vessels.The aim of this study was to evaluate the inter-observer agreement of this 3-step mucosal morphology classification system amongst non-expert endoscopists and to evaluate the appreciated difference in image quality between NBI and white light endoscopy (WLE). Six endoscopists from 6 separate non-university hospitals with no specific experience in BE or advanced imaging techniques independently evaluated magnified still images of 50 areas of BE. They scored the overall, mucosal and vascular imaging quality on a VAS. In addition, the 3 step classification system was scored. The endoscopists first assessed the WLE images, followed by the corresponding NBI images in random order, and finally an evaluation of the WLE images and NBI images together. Assessed independently, the overall imaging quality of WLE received a higher rating than NBI (mean VAS score 7.4 vs. 7.1; $p<0.05$). When WLE and NBI were assessed side-by-side, however, NBI images were scored as having a better overall imaging quality in 75% of the assessments, a better mucosal imaging quality (82%) and vascular imaging quality (82%); $p<0.0001$. The inter-observer agreement for the items of the 3-step classification system was fair to moderate (kappa 0.36 to 0.55). The best agreement was obtained for the presence of irregular mucosal patterns and the worst for scoring the presence of abnormal blood vessels. There were no notable differences in inter-observer agreement between the different techniques used for scoring the items of the classification system.
Conclusion: When directly compared with WLE, NBI was appreciated as a better imaging modality for magnified still images of BE. The inter-observer agreement of the non-expert endoscopists for assessing 3-step classification model was fair to moderate. This may be considered a promising result given the relative inexperience of the endoscopists with NBI and the 3-step classification system of mucosal morphology.

Sporadic duodenal adenoma and colorectal neoplasia

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Sporadic duodenal adenoma is an uncommon finding and data are sparse. A few studies have suggested an association between sporadic duodenal adenomas and colorectal neoplasia, but the extent of this association is unknown. The aim of the present study was to determine the presence of colorectal neoplasia in patients with sporadic duodenal adenoma.

Patients with a diagnosis of duodenal adenoma in the period between 1991 and April 2006 were identified using the digital endoscopic report system of an academic and a regional hospital. Patients were included if the diagnosis of duodenal adenoma was confirmed by histology. Patients with duodenal carcinoma, patients with, or belonging to, familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC) kindreds were excluded. Clinical records for identified patients were examined for diagnosis of colorectal neoplasia. Location, size and histology were recorded for both duodenal adenoma and colorectal neoplasia. Patients with multiple lesions were classified according to the most advanced lesion found. Advanced adenomas (duodenal and colorectal) were defined as having a size $\geq$ 10 mm, the presence of a villous component or high-grade dysplasia.

A total of 60 patients with sporadic duodenal adenomas were identified. The mean age of patients was 66 years, 57% was male. Adenomas were located in the duodenal bulb (25%), second part of the duodenum (38%) and ampullary region (37%). Large duodenal adenomas ($\geq$ 10 mm) were found in 30 patients (50%). The majority of patients had tubular adenomas (43%), 11 (18%) patients had an adenoma with a villous component and in 7 patients (12%) high-grade dysplasia was reported. Overall, 38 patients (63%) had advanced adenomas.

Colonoscopy was performed in 24 patients (40%). Colorectal neoplasia was found in 14 of these 24 patients (58%). Colorectal neoplasia was most commonly located in the rectum (29%) and sigmoid (29%). Large colorectal neoplasia ($\geq$ 10 mm) was observed in 5 patients (36%). Colorectal cancer was detected in 2 patients (14%), advanced colorectal neoplasia in 6 patients (43%) and non-advanced colorectal neoplasia in 6 patients (43%).

Conclusions: The majority of duodenal adenomas are diagnosed as advanced lesion. The presence of colorectal neoplasia in patients with sporadic duodenal adenoma is substantial. Colonoscopy is not routinely performed in patients with sporadic duodenal adenomas, but should be considered in these patients.

How effective is the disinfection of endoscopes?

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Several endoscopy related outbreaks have been reported. Transmission tends to be incidentally identified when associated with an unusual species or a microorganism (m.o.) with uncommon resistance profile. Spread of common m.o.'s may remain unrecognized. Therefore, we designed a microbiological surveillance system with standard sampling intervals. The system includes the endoscopes and, if indicated, the automatic Washer Disinfectors (WD's).
Aims of the research were: To evaluate the efficacy of the cleaning and disinfection procedure of endoscopes; To assign disinfection problems to individual endoscopes and/or WD's
The following methods were used: Surveillance protocol, anterograde and retrograde sampling of endoscopes; Decision scheme; Random Amplified Polymorphic DNA; Scanning Electron Microscopy on the exchanged sheaths of channels and the elevator wire of frequently contaminated endoscopes
Over a time period of 29 months we found an increasing number of endoscopes positive for *C. non-albicans.* These yeasts were also isolated from the WDs. However, directly after the once daily autodisinfection process in the morning no yeasts were found, but after regular cycles during the working day Candida cells appeared in the WD's. The number of tests positive for *C. parapsilosis* varied from 2 of 30 to 15 of 37 samples of seven frequently used endoscopes. The range of CFU/ml was between 1-10 to 3000 for endoscopes and 0.02 to 0.06 for the WDs. First results of DNA fingerprinting showed the same banding pattern for all analysed *C parapsilosis* strains isolated from the endoscopes, the WDs and one patient.
31% of all surveillance cultures (retrograde) were positive for different bacteria or fungi. Generally retrograde sampling was nearly 4 times more sensitive than anterograde sampling. For yeasts the sensitivity of retrograde sampling was even 9 fold higher.
Biofilmforming in endoscopes was found by Electron Microscopy.
Conclusions: Retrograde sampling is much more sensitive than anterograde sampling;
Without retrograde sampling the structural problem with *C. parapsilosis* would not have been detected; Biofilmformig in endoscopes is not prevented by the disinfection procedure; We were able to show the likelihood of cross-contamination between endoscopes and the WD's. Transmission of m.o.'s in an endoscopy center is despite a well-controlled disinfection process likely to occur and may pose a risk for patients.

Assessment of tumor growth in relation with increase of future remnant liver volume and function in patients undergoing preoperative portal vein embolization.

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Preoperative portal vein embolization (PVE) is an option in patients requiring liver resection in whom the estimated future remnant liver (FRL) volume is too small on CT scan. PVE induces atrophy of the embolized, tumor bearing lobe while compensatory hypertrophy occurs of the non-embolized lobe, hereby increasing volume and function of the FRL. The time interval between PVE and resection, is mainly determined by the time needed to reach sufficient hypertrophy of the FRL. Safe resection can be performed if the FRL exceeds 30% of total liver volume. However, there is evidence that tumor growth is accelerated after PVE, creating a dilemma in terms of optimal waiting time until resection.Increase of function of the non-embolized liver segments may be more advanced than increase of volume after PVE. This implies that the time period until operation may be shorter than suggested by the increase of volume. However, few methods are available to measure function of the FRL after PVE. Hepatobiliary scintigraphy (HBS) using 99mTc- mebrofenin is a quantitative method for evaluating total and regional liver function. The aim of this study was to assess tumor growth after PVE, and to compare increase of volume and increase of function of the non-embolized lobes, using CT volumetry and HBS, respectively.PVE was performed in eleven patients from 2005 till 2006. CT volumetry was used to measure tumor volume and liver volume. HBS was used to determine liver function. Before PVE, total liver volume, tumor volume and total liver function, as well as estimated FRL volume and FRL function were determined. Three to four weeks after PVE, CT volumetry was performed to measure the increase of volume of the FRL and tumor growth in the non-embolized lobe. HBS was used to measure liver function. Eight patients had measurable tumors in the liver. Seven patients showed increased tumor growth after PVE(23.5 %) One patient with adenomatosis showed a decrease in tumor volume.Increase of function of the FRL (41.3 %) measured with HBS was significantly ($p<0, 05$) greater than increase of volume (29.9% increase) 3-4 weeks after PVE. This study confirms that tumor load is increased after PVE. Therefore, time interval between PVE and resection should be limited. Furthermore, this study shows that increase of function is more advanced than increase of volume. Additional functional assessment of the FRL after PVE using HBS may reduce the time period between PVE and liver resection.

Health Related Quality of Life of hepatitis C patients in the DITTO-study

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Background: Treatment with PEG-interferon and Ribavirin in chronic hepatitis C virus (HCV) is associated with a decrease in Health Related Quality of Life (HRQL) due to side-effects. Current guidelines lead to under-treatment in some and over-treatment in other individuals. The DITTO-study, a multi-center randomized clinical trial, compared PEG-interferon α-2a (180 µg qw) plus Ribavirin (1000-1200 mg qd) (standard therapy (ST)) with a dynamically individualized treatment schedule (IT) according to early virological response (week 4) in order to increase sustained virological response (SVR), optimizing available drugs, treatment duration and quality of life. Aims: To assess differences in HRQL before and after therapy, corrected for treatment, treatment response and baseline characteristics. Methods: The Short Form 36 (SF-36) was used to measure quality of life. It contains 36 questions measuring health across eight different dimensions – physical functioning (PF), role limitation because of physical health (RP), social functioning (SF), vitality (VT), bodily pain (BP), mental health (MH), role limitation because of emotional problems (RE) and general health (GH). A combined score can be generated from 0 to 100, where 100 indicates "good health". Of all 273 patients 192 completed the SF-36 at baseline 0 and 120 patients completed the SF-36 at 24 weeks after treatment (end of follow-up, EOF), with 120 paired samples.
Results: The differences in the eight dimensions between EOF and baseline did not differ significantly between ST and IT, regardless response to therapy. However, between EOF and baseline the GH score in all non-responders to therapy worsened (mean: – 6.3) whereas in all patients with a sustained response the GH score improved (mean: + 6.1) ($p = 0.019$). Scores of BP and SF worsened at EOF compared to baseline in women and improved in men (significantly different). Age group, fibrosis score nor genotype had a significant impact on HRQL.
Conclusion: Dynamically individualized treatment does not improve HRQL. Obtaining a sustained virological response to therapy leads to a improvement of general health.

Double-dose peginterferon-α2b induction plus ribavirin in chronic hepatitis C patients with previous nonresponse to interferon monotherapy or combination therapy with ribavirin.

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Background/aim: Standard dosed peginterferon/ribavirin therapy has a limited success in the treatment of chronic hepatitis C patients who failed to achieve a sustained response (SVR) with previous therapy. Potential options to increase SVR rates, are double-dose peginterferon induction therapy and prolonged treatment. Higher dosing of peginterferon might yield stronger impairment of health-related quality of life (HRQL).
Methods: We randomized 53 patients, who previously failed to standard interferon-α monotherapy or combination therapy with ribavirin, to a high dose induction regimen combined with treatment prolongation (peginterferon-α2b 3.0 µg/kg QW 12 weeks → 2.0 µg/kg QW 12 weeks → 1.5 µg/kg QW 48 weeks) or standard regimen (peginterferon-α2b 1.5 µg/kg QW 48 weeks). Treatment arms were stratified for genotype (genotype 1 or 4 vs. others) and response to previous treatment (responder-relapser vs. non-responder). All patients received daily 1000-1200 mg ribavirin, based on body weight. The short-form 36 (SF-36) health survey was used at six different timepoints (t=0, t=4, t=24, t=48, t=72 and t=96) in order to evaluate HRQL.
Results: On intention-to-treat basis, the rate of SVR was 44% for the experimental regimen, compared to 37% for the standard regimen (p=0.62). Virological response rates at week 12 (>2log drop of HCV RNA) were 61% vs 60%, at week 24 (HCV RNA negative) were 52% vs 53% and at end of treatment 48% (wk 72) vs 53% (wk 48), respectively. All p-values were not statistically significant. Early discontinuation due to serious adverse events was needed in 2 patients on experimental treatment. Two other patients on experimental treatment and 3 on standard treatment were lost to follow-up. Dose reductions of peginterferon-α2b were needed in 3 patients on experimental treatment and 5 patients on standard treatment. HRQL declined during antiviral therapy but returned to or exceeded baseline levels within 24 weeks of post-treatment follow-up. There were no significant differences in HRQL between both groups.
Conclusions: Overall SVR rates in this pilot study were higher than previously reported. However, double-dose induction and prolongation of peginterferon-α2b therapy combined with ribavirin did not improve outcome when compared to standard peginterferon-α2b/ribavirin therapy. Both treatment regimens were tolerated well and there were no differences in early treatment withdrawal. There was no peginterferon dose-related HRQL impairment.

Modeling of pharmacokinetics and viral kinetics in HBeAg-positive chronic hepatitis B treated with pegylated interferon alpha-2b

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Mathematical models to describe pharmacokinetics and viral kinetics may improve the understanding of the mechanisms of action of pegylated interferons and therefore contribute to the development of different treatment regimens.
In 96 HBeAg-positive chronic hepatitis B patients treated with pegylated interferon alpha-2b (PEG-IFN) 100 µg/week with or without lamivudine 100 mg/day, IFN concentrations were measured at day 0, 1, 2, 3, 4 and 7 of treatment. HBV DNA levels were measured in a subgroup of 19 patients in each treatment arm. The IFN concentration was analysed with a non-linear mixed model using an absorption and elimination model. Mixed modeling uses a group-wise analysis with subject specific random effects for the rate of elimination (k_e), the rate of absorption (k_a), the bioavailability (F), the volume of distribution (V_d) and the delay between administration and maximal drug concentration (τ). Assuming that the effectiveness depends on the varying drug concentration in the first week of treatment, the predicted effectiveness over time could hereafter be incorporated in an expanded non-linear mixed model to fit the viral load in patients treated with PEG-IFN monotherapy.
There were no differences in IFN concentration in the PEG-IFN monotherapy and PEG-IFN plus lamivudine therapy group at any time point. Using this non-linear mixed modeling, we were able to adequately fit 95% (91/96) of the pharmacokinetics in either treatment arm and all (19/19) viral kinetics data in the PEG-IFN monotherapy arm. The population mean of k_e was 0.42 per day (with an individual interquartile range of 0.36-0.48), of k_a 2.36 per day (1.39-3.41), of F/V_d 1.02 (0.72-1.60) with a τ of 1.06 day (0.87-1.43). There was a correlation between pharmacokinetic constants k_a and F/V_d and the body surface area (BSA) with correlation coefficients of -0.24 (p=.019) and -0.30 (p=.003), respectively. Viral load was minimal 3.7 days (3.25-3.90) after administration of PEG-IFN alone, with a rebound thereafter.
In conclusion, an adequate fit of pharmacokinetics can be made with non-linear mixed modeling techniques using IFN concentrations from the first week of PEG-IFN treatment and this model can be used to fit viral load during PEG-IFN therapy. Based on these findings, PEG-IFN administration every 4 days and weight-based dosing can be considered to optimize drug availability.
Disclosure Zeuzem: Schering Plough and Roche: Consultant and clinical investigator, member of speakers bureau

Early peginterferon alpha-2b induced HBeAg loss results in increased rates of HBsAg loss and undetectable HBV DNA

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Long-term follow-up studies of interferon-alpha in chronic HBV have shown improved outcome in patients with HBeAg loss compared to those without. Recently, serum HBV DNA below 10,000 copies/ml was found to be independently associated with decreased risk of developing cirrhosis, hepatic decompensation and hepatocellular carcinoma. The aim of this study was to investigate the relation between timing of peginterferon alpha-2b (PEG-IFN α-2b) induced HBeAg loss, and decline in serum HBV DNA and HBsAg loss. A total of 266 patients participating in a global randomized controlled study were assigned to 52 weeks of PEG-IFN α-2b alone (100µg weekly, n=136) or in combination with lamivudine (100mg daily, n=130), and were followed for 26 weeks after therapy. Treatment groups were comparable regarding baseline characteristics. Rates of HBeAg loss we comparable in patients treated with PEG-IFN α-2b alone or in combination with lamivudine at week 78 (36% and 35%, p=0.91), as well as HBV DNA <400 copies/ml (7% and 9%, p=0.43). Patients with HBeAg loss were more likely to have HBV DNA below 10,000 copies/ml at week 78 than patients without (49% vs. 2%, p<0.001), as well as HBV DNA < 400 copies/ml (22% vs. 0%, p<0.001). Among patients with loss of HBeAg at week 78, 56% lost HBeAg before week 32, 24% between week 32 and 52, and 20% during post-treatment follow-up (week 52-78). HBsAg loss at week 78 occurred in 17% of patients with HBeAg loss. HBsAg loss occurred significantly more often in patients with HBeAg loss before week 32 than in those with late HBeAg loss (30% vs. 4%, p=0.03). HBeAg loss before week 32 was found to significantly increase rates of HBV DNA <10,000 at week 78 compared to late HBeAg loss (62% vs. 16%, p<0.001), as well as HBV DNA <400 copies/ml (32% vs. 9%, p=0.04). Off-treatment sustainability of HBeAg loss also tended to be higher among those with an early HBeAg loss (75% vs. 64%, p=0.25). Baseline HBV DNA was lower in patients with HBeAg loss than those without, but comparable in the subgroups with HBeAg loss.
Conclusions: PEG-IFN α-2b induced HBeAg loss before week 32 results in significantly higher rates of HBsAg loss and greater viral decline at week 78 compared to late HBeAg loss.

Peginterferon alpha-2b is well tolerated and leads to high virological and histological response rates in chronic hepatitis B patients with advanced fibrosis.

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HBeAg seroconversion and serum HBV DNA below 10,000 copies/ml are associated with decreased risk of developing cirrhosis, hepatic decompensation and hepatocellular carcinoma. Since peginterferon (PEG-IFN) therapy may precipitate dangerous immunological flares, patients with advanced fibrosis are often refrained from this therapy. The aim of this study was to investigate the efficacy and safety of PEG-IFN α-2b in patients with advanced fibrosis. A total of 266 patients participating in a global randomized controlled study were assigned to 52 weeks of PEG-IFN α-2b alone (100µg weekly, n=136) or in combination with lamivudine (100mg daily, n=130), and were followed for 26 weeks after therapy. Treatment groups were comparable regarding baseline characteristics and all outcome parameters. Two-hundred-thirty-nine patients who had a liver biopsy taken at baseline were included in this analysis. Advanced fibrosis was defined as Ishak fibrosis score of 4 to 6. Seventy of the 239 patients had advanced fibrosis (29%). Rates of HBeAg seroconversion, HBsAg seroconversion, improvement of necroinflammation and HBV DNA <400 copies/ml tended to be higher in patients with advanced fibrosis compared to those without. Improvement of fibrosis at week 52 was observed significantly more frequent in patients with advanced fibrosis compared to those without (66% vs. 26%, p<0.001), as well as and HBV DNA <10,000 copies/ml at week 78 (30% vs. 17%, p=0.04). Most adverse events occurred equally in those with or without advanced fibrosis. Fatigue, anorexia and thrombocytopenia were more prevalent among those with advanced fibrosis (p<0.01). Necessity for dose reduction or discontinuation was comparable for both patient groups. Serious adverse events occurred in 4% of patients with advanced fibrosis and 5% of those without. One patient with advanced fibrosis had temporarily elevated bilirubin, which resolved after scheduled discontinuation of therapy. No other signs of liver failure were encountered.
Conclusions: PEG-IFN is safe and leads to high rates of virological and histological response in HBeAg-positive patients with advanced fibrosis. Since PEG-IFN therapy results in sustained off-therapy response, patients with advanced fibrosis and fully compensated liver disease should not be excluded from PEG-IFN treatment.

Expression of lipo-oligosaccharide ganglioside mimics protects *Campylobacter jejuni* from phagocytosis by human THP-1 monocytes

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Campylobacter jejuni is the predominant cause of bacterial gastro-enteritis in industrialized countries and poses a significant socio-economical burden. *C. jejuni* can induce post-infectious immune-mediated polyneuropathy (Guillain-Barré Syndrome, GBS) through molecular mimicry between the bacterial lipooligosaccharide (LOS) and gangliosides expressed on nerve cells. However, not all *C. jejuni* strains that express ganglioside-mimics induce GBS and the biological significance of ganglioside expression by *C. jejuni* remains to be elucidated. Sialic acid, which is a key component of gangliosides, is a specific ligand for sialic acid-binding immunoglobulin-like lectins (Siglecs) that provide inhibitory signals to cells of the immune system. Monocytes and macrophages are important in the defence against C. jejuni, but little is known about the molecular mechanism involved. Some C. jejuni strains are resistant to phagocytosis and the majority of strains is able to survive in monocytes or macrophages for several days. Here, we demonstrate that expression of ganglioside mimics in the LOS protects *C. jejuni* against phagocytosis and killing by human monocytes.
In ELISA, clinical *C. jejuni* isolates and *C. jejuni* sialyltransferase-II (*cstII*) knock-out mutants, which lack ganglioside mimics, were studied for binding to human Siglecs. Subsequently, uptake and survival of *C. jejuni* 81-176, GB19 ($GD3^+$) and GB19*⊿cstII* ($GD3^-$) in the human monocytic cell line THP-1 was assessed.
C. jejuni strains with ganglioside mimics in their LOS specifically bound to Siglecs that are expressed on human monocytes and macrophages. The binding pattern of *C. jejuni* to Siglecs reflected their expression of distinct LOS ganglioside mimics. Disruption of *cstII* in *C. jejuni* resulted in loss of expression of ganglioside mimics and GB19*⊿cstII* was not able to bind Siglecs any more. *In vitro*, phagocytosis of *C. jejuni* 81-176 and GB19 by THP-1 monocytes occurred at a low level. However, uptake of GB19*⊿cstII* by THP-1 cells was increased 100-fold, as compared to uptake of the GB19 wild type strain. *Conclusion:* Our results suggest that LOS ganglioside expression suppresses the uptake and killing of *C. jejuni* by human phagocytes, which may enhance duration of the intestinal infection. These data provide new insight in the immune-pathology of *C. jejuni*-associated gastro-enteritis and may open up the way for therapeutic intervention and prevention of severe post-infectious complications.

The TNF-β polymorphism NcoI is associated with an increased risk of developing Barrett's esophagus and esophageal adenocarcinoma in gastro-esophageal reflux disease

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TNF is a key cytokine in inflammatory processes. Genetically determined differences (polymorphisms) in the promoter region of the TNF-β gene are associated with high TNF expression levels, and an increased risk of cancer development. Barrett's esophagus (BE) is a pre-malignant condition of the esophagus which could lead to esophageal adenocarcinoma (EAC) in patients with gastro-esophageal reflux disease (GERD). In the present study, we investigated the polymorphism TNF-β (*NcoI*) in patients with reflux esophagitis (RE), BE and EAC.
DNA was obtained from 197 healthy controls (100% Caucasian; mean age 57 ± 14y; 59% male), 305 patients with endoscopically confirmed RE (100% Caucasian; mean age 55 ± 13y; 55% male), 257 patients with BE (100% Caucasian; mean age 61 ± 12y; 69% male), with a segment of specialized intestinal metaplasia of ≥2 cm, and 128 patients with EAC (100% Caucasian; mean age 63 ± 10y; 82% male). The gene polymorphism of the TNF-β (*NcoI*) was determined by modified TAQMAN assays. Logistic regression was used to calculate odds ratio (OR) and 95% confidence intervals (CI) for variant genotypes.
The frequency of TNF-β (*NcoI*) heterozygosity was increased in BE (p=0.020; OR=1.596; 95% CI:1.071-2.377) and EAC (p=0.022; OR=1.663; 95% CI:1.037-2.667), but not in RE (p=0.178; OR=1.225; 95% CI:0.833-1.803) compared to controls, meaning that this polymorphism predicts a 1.6-fold increased risk of developing BE and EAC.
Conclusions: The TNF-β (*NcoI*) polymorphism is associated with an increased risk for the development of BE and EAC. This suggests that anti-inflammatory measures could indeed be useful for the prevention of neoplastic changes in GERD patients.

Matrix metalloproteinase-9 mediated VEGF release contributes to neo-angiogenesis in colon cancer

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Angiogenesis plays a major role in the outgrowth and metastasis of colon carcinomas. Vascular Endothelial Growth Factor (VEGF) is considered the primary angiogenetic factor for solid tumours. Matrix metalloproteinase-9 (MMP-9) is involved in the degradation of extra-cellular matrix components, consequently promoting tumour cell invasion. Recent in vitro studies indicate a much broader spectrum of MMP-9 activity. MMP-9 is apparently also involved in the modulation of regulators of cell growth and chemotaxis. In the present study, we evaluated a possible role for MMP-9 in the release and activation of VEGF in colon cancer.Immunohistochemical stainings were performed to determine the expression of VEGF and MMP-9 in tumour tissue of colon carcinoma patients and revealed an enhanced expression of both markers in vivo. The presence of unoccupied VEGF-receptors in the same tissues was identified using radio-labeled human VEGF. Strikingly, binding of VEGF was only observed in adjacent normal mucosa, suggesting that the majority of these receptors is occupied in tumour tissue.The direct effect of MMP-9 on VEGF was evaluated in vitro. Addition of MMP-9 to 3-dimensionally growing HT29 colon carcinoma cells resulted in dose-dependent release of VEGF into the medium, as determined by ELISA. Moreover, the medium from the MMP-9 treated HT29 cells induced sprout formation of endothelial cells in a novel 3-dimensional angiogenesis model in a similar way compared to recombinant human VEGF. Addition of an MMP inhibitor significantly reduced sprout size, whereas MMP-9 alone hardly induced sprout formation.
Conclusions: The expression of both MMP-9 and VEGF is enhanced in colon carcinoma tissues. Our in vitro experiments suggest a role for MMP-9 in the release and activation of VEGF, a growth factor involved in tumour neo-vascularisation in colon cancer. Future experiments should verify whether enhanced expression of MMP-9 in colon cancer tissue indeed correlates with increased VEGF induced neovascularisation in vivo.

Dose-dependent influence of 5-ASA on thiopurine metabolism

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Introduction: Thiopurines are frequently administered immunosuppressive drugs in the treatment of inflammatory bowel disease (IBD). A substantial number of patients is unable to benefit from thiopurine therapy due to the development of inadequate metabolites levels. Several studies indicated that 5-aminosalicylates (5-ASA) may influence the metabolism of thiopurines but conclusions were restricted due to the number of patients or study design. Aims & MethodsWe prospectively investigated the influence of two different 5-ASA (Pentasa®) dosages (2 gr/day followed by 4 gr/day) on thiopurine metabolism. IBD patients on mono-therapy thiopurines were included and received consecutively the two different 5-ASA regimes. 6-Thioguaninenucleotide (6-TGN) and 6-methylmercaptopurine (6-MMP) levels were determined before 5-ASA therapy (t=1), after 4 weeks of 2 gr/day (t=2), after 4 weeks of 4 gr/day (t=3) and after at least 4 weeks after cessation of 5-ASA therapy (t=4).
Results: Sixteen IBD patients on steady state azathioprine therapy, dosages 2 - 2½ mg/kg, were included. Mean 6-TGN levels during the different regimes were 224 (t=1), 302 (t=2), 351 (t=3) and 248 (t=4) pmol/8x10E8 RBC, respectively. Mean 6-MMP levels were 2686 (t=1), 3161 (t=2), 2100 (t=3) and 2756 (t=4) pmol/8x10E8 RBC, respectively. Baseline 6-TGN levels increased significantly after 2 gr/day (P=0.006) and after 4 gr/day (P<0.001). The 6-TGN level at t=3 was significantly higher than at t=2 (P=0.036). A rise in 6-TGN levels was observed in 88% (t=2) and 100% (t=3) of patients. 6-TGN levels increased with 42% (SD 47%) (t=2) and 67% (SD 55%) (t=3), respectively. No significant variations in 6-MMP levels were observed.
Conclusion: 6-TGN levels during thiopurine therapy increase in a dose-dependent manner during 5-ASA co-administration. However, 5-ASA has no influence on 6-MMP levels. Our results warrant further studies on 5-ASA use in IBD patients who develop inadequate 6-TGN levels during thiopurine therapy.

Surveillance for colorectal carcinoma in patients with inflammatory bowel disease: are AGA and BSG guidelines adequate?

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Patients with inflammatory bowel disease (IBD) are at increased risk of colorectal cancer (CRC). To detect dysplasia or asymptomatic CRC, both American (AGA) and British (BSG) surveillance guidelines recommend starting surveillance colonoscopies after 8-10 years of disease duration for extensive colitis and after 15-20 years for left sided colitis, assuming that patients do not develop CRC within these intervals. Strong clinical evidence for these intervals is not available. Furthermore, several cases in our hospital developed CRC within these intervals. The aim of our study was to assess the amount of patients that develop IBD-associated CRC before the first surveillance colonoscopy takes place. All patients in our medical centre with IBD-associated CRC from January 1990 until June 2006 were selected by using a nationwide pathological anatomical automated archive (PALGA). Observed intervals between the occurrence of IBD and CRC were compared with guideline intervals as recommended by the AGA and BSG.We identified 29 patients with IBD-associated CRC, 14 (48%) had ulcerative colitis, 15 (52%) had Crohn's disease, 18 (62%) were male and 11 (38%) were female. The median [range] ages of diagnosis of IBD and CRC were 29 [11-82] and 47 [23-82] years respectively. Most CRCs developed in the distal colon, i.e. 76% of the CRCs were found in the rectum (15/29), sigmoid (5/29) and splenic flexure (2/29).When the observed intervals between the diagnoses of IBD and CRC were compared with the 8 (extensive colitis) or 15 year (left sided) guideline intervals, 7 of 29 (24%) patients developed CRC before the first surveillance endoscopy is recommended. If onset of IBD symptoms was taken as starting point for the interval, 5 of 29 (17%) patients developed CRC before the first surveillance colonoscopy should have been performed.When comparing the observed IBD-CRC intervals with the 10 (extensive colitis) or 20 year (left sided) guideline intervals, 9 of 29 (31%) patients developed CRC before surveillance is initiated. For onset of IBD symptoms this was 7 of 29 (24%) patients.
In conclusion, in this retrospective single-centre study a minimum of 17% and a maximum of 31% of our IBD-associated CRC patients developed cancer before the first surveillance colonoscopy is recommended. If these findings are confirmed in a larger study, which is presently being undertaken in all university medical centres in the Netherlands, we believe surveillance should be started earlier.

A Panel of genes in pediatric-onset inflammatory bowel disease compared with healthy controls and adult-onset inflammatory bowel disease.*

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Genetic susceptibility probably plays an important role in pediatric-onset inflammatory bowel disease (IBD). We determined the frequency and phenotypic correlations of the major known IBD related NOD2/CARD15, TLR 4, DLG5 and OCTN gene mutations in 103 (94 for OCTN and DLG5) Dutch pediatric IBD patients (mean age 12.0 years, range 0.5-18.0); 50 boys). A comparison with healthy controls and adult-onset IBD patients was made.A statistical association of carriership of R702W mutation was found with pediatric-onset Crohn's disease (CD) (14 [19.5%] versus controls 17 [6.3%]; p= 0.0027). A nearly statistical association of 3020Cins mutation was found with pediatric-onset CD (10 [13.9%] versus controls 20 [7.3%]: p =0.060). In the pediatric-onset CD cohort homozygosity for the 3020Cins mutation was noted in 3 patients (4.2%) and in 2 out of 343 (0.6%) adult-onset CD patients (p=0,01). A statistical association of carriership of the OCTN rs3792876 was found with pediatric-onset CD (12 [18.2%] versus controls 38 [13.3%]: p=0.009). Homozygosity for this polymorphism was significantly increased in pediatric-onset CD patients compared to adult-onset CD patients (4 [6.1%] versus 2 [0.7%]; p=0,006).DLG5, rs 2165047 was associated with UC although not statistically significant (p=0.087). No significant associations of TLR4 mutations were found. Genotype carrier frequencies were calculated in subgroups of pediatric-onset CD. 3020Cins polymorphism was associated with ileal disease and stricturing CD and a positive family history of IBD. DLG5 rs2165047 is associated with perianal disease.
Conclusions: The occurrence of pediatric-onset CD was found to be associated with the NOD2/CARD15 R702W and OCTN rs3792876 mutations. Homozygosity for the NOD2/CARD15 3020Cins and OCTN rs3792876 mutation was significantly associated with pediatric-onset CD versus adult-onset CD. Several genotype-phenotype correlations in pediatric-onset IBD exist. These data stress the importance of genetic susceptibility research in large pediatric-onset IBD cohorts in order to find new genes and to establish the influence of these mutations on disease behaviour and treatment.

Bi-allelic MUTYH mutations are found in a significant number of Dutch MUTYH-associated polyposis coli (MAP) patients, but not in patients with between 1-10 polyps or HNPCC.

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Our objective was to assess the prevalence of MUTYH mutations in patients with polyps and/or colorectal cancer, and compare them with healthy controls. We performed MUTYH mutation analysis in polyposis patients previously tested negative for APC mutations (n=170); patients with between 1-10 polyps (n=694); hereditary nonpolyposis colorectal cancer patients (HNPCC)(n=67) and healthy controls(n=653). Furthermore we describe the clinical phenotype of MUTYH associated patients (MAP). In polyposis and HNPCC patients sequence analysis of the whole MUTYH gene was done. In patients with 1-10 polyps and healthy controls TaqMan SNP analysis was done for the most prevalent MUTYH mutations, Y165C, G382D and P391L. Bi-allelic MUTYH mutations were identified in 40 (24%), and heterozygote carriers in 4 (2,5%) of the 170 polyposis patients. In patients with 1-10 adenomas and HNPCC patients no bi-allelic carriers were found and 15 out of 694 (2,2%) respectively 3 out of 67 (4,5%) heterozygote carriers were found. All mutations found in these two groups were Y165C and G382D mutations. In controls no bi-allelic carriers were found and 15 (2,2%) MUTYH heterozygote carriers were found. In the polyposis patient group the same percentage of bi-allelic carriers was found in patients with 10-99 polyps or 100-1000 polyps (29% in both groups). Colorectal cancer was found in 26 of the 40 (65%) MAP patients within the age range of 21-67 years. Complete endoscopic reports were available for 16 MAP patients and revealed five cases with gastro-duodenal polyps (31%), one of whom also presented with a duodenal carcinoma. Breast cancer occurred in 18% of female MAP patients, significantly more than expected from national statistics.
Conclusions. MUTYH mutations explain a large proportion of polyposis patients previously tested negative for APC mutations. There was no (significant) difference in the number of MUTYH heterozygote carriers in patients with 1- 10 polyps compared to that in healthy controls. In HNPCC patients a non significant higher prevalence of MUTYH mutations (4,5%) as compared to controls (2,3%) was found. Polyp numbers in 40 MAP patients were equally associated with the attenuated and classical polyposis coli. Two-thirds of the MAP patients had colorectal cancer, 95% of whom were older than 35 years, and one-third of a subset of patients had upper gastrointestinal lesions. Our findings warrant endoscopic screening every 2 years for MAP patients, starting at age 20-25 yrs.

Increased risk of colorectal neoplasia in asymptomatic liver transplant recipients.

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Controversy exists whether liver transplant recipients carry an increased risk of colorectal neoplasia that should warrant colorectal cancer screening. We previously found an increased risk of colorectal cancer in liver transplant recipients compared to the general population (J Hepatology 2001). The aim of this study was to determine the prevalence of colorectal neoplasia in asymptomatic liver transplant recipients. Asymptomatic liver transplant recipients who had a screening colonoscopy at least 5 years after liver transplantation were retrospectively evaluated for the prevalence of colorectal neoplasia. Patients with previous colorectal adenomas or carcinomas were excluded. Advanced neoplasia was defined as an adenoma at least 1 cm in diameter and/or with villous features and/or high-grade dysplasia, or cancer. Findings at colonoscopy were categorized according to the most advanced lesion. Results were compared with prevalence data from the literature in screening colonoscopy studies in asymptomatic average-risk persons (including a Dutch cohort, de Jong et al, Am J Gastro 2005), adjusted for age. Potential risk factors for colorectal neoplasia were analyzed.92 asymptomatic liver transplant recipients had undergone a screening colonoscopy at a median age of 53.5 years (range 35.8-71.2). Adenomas were found in 21.7 % of patients. Advanced neoplasia was diagnosed in 8.7 % of patients, which is relatively high when compared with data from the literature in average-risk populations. No cancers were found. Compared with the Dutch control cohort, the relative risk (RR) in patients under 50 years of age for neoplasia was 3.6 (95 % confidence interval 1.1-12.2, $p < 0.05$) and 8.9 (1.7-46.3, $p < 0.01$) for advanced neoplasia. Also in patients aged 50-59, an increased RR was observed for advanced neoplasia in liver transplant recipients, varying between 2.5 and 9.5, when compared with data from the literature. The risk of colorectal neoplasia was associated with the initial immunosuppressive regimen.
In conclusion, liver transplant recipients have an increased risk of developing colorectal neoplasia, especially advanced neoplasia, in comparison with average-risk populations, possible as a consequence of the use of immunosuppressive agents. Offering screening colonoscopy to asymptomatic liver transplant recipients should strongly be considered.

Genetic Aspects of Chronic Pancreatitis.
Final report Maag Lever Darm Stichting projectno. WS 00-21

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Background: Chronic pancreatitis (CP) is associated with alcohol abuse, smoking and other dietary or environmental factors. We investigated genetic variations, resulting in variable rates of detoxifying enzymes and also assessed the levels of antioxidant capacity and oxidative damage in CP patients.
Methods: In large cohorts of patients with different types of CP and healthy control subjects genetic polymorphisms were determined by PCR-RFLP. To evaluate the degree of oxidative stress we measured products of oxidative damage (protein carbonyls and TBARS), thiols and non-enzymatic antioxidant capacity and the production of reactive oxygen species.
Results: The GSTM1 null genotype was significantly less common in patients with alcoholic CP and was identified as a protective factor for this group of CP patients, whereas the polymorphism in intron6 CYP2E1, encoding a less efficient microsomal alcohol-metabolizing enzyme, increases the risk for alcoholic CP. In patients with idiopathic CP the PON1-192Q allele, encoding low antioxidant enzyme activity, was significantly more common. Nevertheless, we failed to detect associations between CP and genetic polymorphisms in other biotransformation enzymes such as UDP-glucurunosyltransferases but found evidence that associations between CP and these enzymes found in earlier studies were caused by PCR bias. In addition a lower antioxidant capacity and more oxidative damage was established in CP patients.
Conclusions: We may conclude that genetic predisposition for CP might be partly the result of polymorphisms in detoxification enzymes. Mutation detection can assist in early diagnosis and helps to determine the aetiology of CP. Besides, knowledge on specific polymorphisms will help understanding of gene-environment interactions and knowledge of functional consequences of gene defects may help developing new therapeutic interventions. The lowered antioxidant capacity and increased oxidative damage suggest that oxidative stress also might contribute to the pathogenesis of CP, which may be a rationale for intervention with antioxidant therapy.

Polyp multiplicity and colorectal cancer. Over 10^7 simulations to meet scientific standards?

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Modelling of life time adenoma incidences enables the development of optimal scenarios for colorectal screening. Such a model can only be based on autopsy data. Due to the tranversal nature of these data and the need to exclude symptomatic neoplasia we had to account for underrepresentation of colorectal cancers, particularly affecting the data in the oldest age range. To cope with this we proceeded as follows: Model parameters shaping adenoma incidence as a function of age and preexisting number of adenomas were fitted to adenoma prevalences observed in 1000 random samples drawn from a series of 490 subjects autopsied in the Rotterdam area. Projections, based on data up to 70 years only, suggested that adenoma incidences would continue to rise throughout life, while the observations showed a deflection beyond 70 years - more so if adenoma multiplicity increased. Subsequently, a simulation model rendering adenoma “birth years” in a 90 year life span was combined with a time dependent probability function to seek the rate of malignant transformation, which reproduced the incidence of colorectal cancer in the Netherlands. Accurate statistics were estimated to involve over 10^7 simulated lives, at least 10.000 for each sample. Surprisingly the simulation procedure greatly simplified the analysis: The proportion of the known cumulative incidence of colorectal cancer among subjects expected to have >=1, >=2, >=3, >= 4, >=5, [..] adenomas by the age of 85 years averaged 100% (by assumption), 80%, 65%, 50%, 35%, [..] respectively. These figures showed remarkably little variation among the bootstrapped samples and were insensitive to reasonable variations in model assumptions. Correction of model outcomes could thus be based on the above average findings – limiting the number of simulations. Corrected model incidences closely reproduced the deflections of the observations (goodness of fit 0.91-0.99 in 95% of the bootstrapped samples). Conclusion: These findings give strong support to the key result from the model analysis, briefly discussed here: A sensitive screening procedure performed at 50 years will identify a 25% adenoma positive subset of the population, bearing most of the cohort risk of early death from colorectal cancer.

Neoplasia of the rectal stump in patients with inflammatory bowel disease.

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Patients undergoing a subtotal colectomy for therapy-refractory ulcerative colitis or Crohn's disease usually retain a rectal stump for the rest of their life if reconstructive surgery is not feasible. We identified eleven patients with neoplasia in a retained rectal stump and looked for potential risk factors involved in the development of malignancy in these patients. Patients with rectal stump neoplasia (RSN) were identified from inflammatory bowel disease (IBD) databases from 4 University Medical Centres. The demographic and disease specific data of these patients were compared with data from a group of 100 consecutive out-patient clinic IBD patients. The incidence of RSN was found to be associated with a longer duration of disease (319 months ± SD 123.1 vs. 175 months ± SD 117.9, $p<0.01$) and a higher number of exacerbations in the course of the disease (24.8 ± SD 24.9 vs. 3.7 ± SD 5.1, $p< 0.01$). Smoking, PSC, or a family history of colorectal cancer was not found to be associated with an increased risk, nor appeared the use of mesalazine to be protective. Two patients presented with a T1 tumour, 1 patient with a T2 tumour, 5 patients with a T3 tumour and 3 patients with a T4 tumour. Four out of 11 patients appeared to have positive regional lymph nodes, while 2 presented with distant metastases. All patients underwent proctectomy, 4 of whom received preoperative radiotherapy. Five patients died before the end of the study. The mean survival after diagnosis of RSN was 18.4 months (range 2-64 months). The remaining 6 patients had a mean survival of 43.2 months (range 1-106 months) at the end of this study.
Conclusion: Rectal stump neoplasia may be an underestimated complication in colectomized IBD patients. Duration of disease and the number of exacerbations were found to be associated with the development of RSN. We advocate to perform surveillance proctoscopies in all IBD patients with a rectal stump.

The introduction of laparoscopic colorectal surgery in daily practice.

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An analysis of the introduction of laparoscopic colorectal surgery in daily practice, before and after specific training was performed by means of a retrospective and descriptive study.The complete introduction process was divided into three phases: the pioneers phase (August ’02 until August ’04), the course phase (September ’04 until December ’04) and the implementation phase (January ’05 until August ’05). In total 88 out of 255 patients, eligible for laparoscopic surgery, underwent elective laparoscopic colorectal surgery. These patients were analysed for iatrogenic complications, operation time and percentage performed by surgical residents. Furthermore, problems occurring during the introduction of this laparoscopic technique were described.The percentage of elective colorectal procedures performed laparoscopically raised significantly during the three phases from 17% (27/163), to 50% (18/36) and 77% (43/56). During the different phases respectively 30%, 17% and 16% of procedures were converted to an open procedure. In the pioneers phase five iatrogenic complications occurred: two ureter stenosis, a colon lesion, an inferior mesenteric artery bleeding lesion and a renal vein bleeding resulting in secondary splenectomy). In the course phase and implementation phase no iatrogenic complications occurred. The average operation time decreased from 191 to 182 minutes, despite the fact that the percentage of procedures performed by surgical residents raised from 15%, to 22% and to 44% in the respectively phases and despite the fact that the amount of rectum resections raised.
Conclusions: Specific training in laparoscopic colorectal surgery results in a safe and fast introduction of this technique in daily practice and in the training program of surgical residents. Specific training can avoid unnecessary iatrogenic complications.

Ex-vivo sentinel lymph node mapping in patients with colorectal cancer

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One of the most important predictors of survival in patients with colorectal cancer is the lymph node status. However, more than 30% of the patients with a curative resection will develop loco-regional recurrence or distant metastases. A possible reason is an inaccurate or incomplete nodal staging. Sentinel lymph node mapping (SLNM) could be a solution for this problem.
The purpose of this study was to evaluate the feasibility and reliability of ex-vivo sentinel lymph node mapping in patients with colorectal cancer.
In the period January 2006 to June 2006, 35 consecutive patients underwent curative surgery for colorectal cancer. There were 21 patients with a colon tumour and 14 patients with a rectum tumour. Excluded for sentinel lymph node mapping were patients with distant metastases and an unresectable tumour. SLNM was performed within fifteen minutes after the resection. In patients with colon cancer, 0.5-2ml of Patent Blue Dye was injected subserosally. In patients with rectal cancer, the specimen was opened at the anti-mesenteric border and the dye was injected submucosally. The injection sites where then gently massaged for five minutes. The first two to six blue stained nodes were considered to be the sentinel nodes.
The median age was 72 years (range, 39-89 years), ratio man: women 15:20.
Ten of the 14 patients with a rectum tumour underwent neo-adjuvant radiotherapy (25GY) and one patient underwent neo-adjuvant radio-chemotherapy (45 GY and 5 FU/ Leucovorin). The remaining patients had colon cancer and were treated with standard oncological resection.
In 95 % of the patients with a colon tumour and 93 % of the patients with a rectum tumour, at least one sentinel lymph node was found.
There were no patients with a false negative sentinel node. The sensitivity was 100 % with a negative predictive value of 100%. In 23.8% of the patients with a colon tumour and 14.3% of the patients with a rectal tumour the sentinel node was the exclusive site of lymph node metastases.
Conclusion: The technique of ex-vivo sentinel lymph node mapping is technically feasible with high sensitivity and negative predictive value. Although in literature a great difference in success rate and false negative rates is reported, this technique seems to be promising.

Dysplasia in the ileal pouch after restorative proctocolectomy for ulcerative colitis: A systematic review

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The aim of this systematic review is to assess the prevalence of dysplasia after restorative proctocolectomy (RPC) for ulcerative colitis.Electronic databases of Pubmed-Medline, Embase, and the Cochrane Library were searched by two independent reviewers from January 1978 up to May 2006 for any terms describing the combination of dysplasia, RPC and ulcerative colitis. In case of duplicate publications that reported on (parts of) similar patient data, only the most recent article was considered. Quality assessment for the papers was performed. In spite of the retrieving of observational data a metanalysis was attempted calculating the relative risk and the Yates Chi-square for each risk factor.Among 901 papers a total of 23 publications encompassing 2040 patients, with a range of follow-up between 3 and 16 years, met the inclusion criteria. At follow-up endoscopy a mean of four biopsies were taken. Pooled prevalence was 1.23% for indefinite for dysplasia, 0.98% for low grade dysplasia and 0.15% for high grade dysplasia. Dysplasia was located in the ileal pouch (n=37) and in the rectal cuff (n=12). Previous diagnosis of colorectal neoplastic change was a risk factor for developing dysplasia after RPC (RR: 5.76, $p<0.01$), while chronic pouchitis showed less influence (RR: 1.21, $p=0.96$). Long duration of ulcerative colitis, long follow up after RPC and primary sclerosing cholangitis showed also to be significant risk factors for dysplasia development ($p<0.01$).
Conclusions: According to our results the prevalence of dysplasia after RPC for UC is rare and a follow up may be useful in patients with definite risk factors.

Detection of colorectal cancer using MALDI-TOF serum protein profiling

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Purpose: Serum protein profiling is a promising approach for classification of cancer versus non-cancer samples. The objective of our study was to assess the feasibility of mass spectrometry based protein profiling for the discrimination of colorectal cancer patients from healthy individuals. Experimental design In a randomized block design pre-operative serum samples obtained from 66 colorectal cancer patients and 50 controls, were used to generate high-resolution MALDI-TOF protein profiles. After pre-processing of the spectra, linear discriminant analysis with double cross-validation, based on principal component analysis was used to classify the protein profiles. Results A total recognition rate of 92.6%, a sensitivity of 95.2% and a specificity of 90.0% for the detection of CRC was shown. The area under the curve of the classifier was 97.3%, which demonstrates the high, significant separation power of the classifier. The first 2 principal components account for most of the between-group separation.
Conclusions: Double cross-validation shows that classification can be attributed to information in the protein profiles rather than to chance. Although preliminary, the high sensitivity and specificity indicate the potential usefulness of serum protein profiles for the detection of colorectal cancer.

Nutritional management for acute pancreatitis: adherence to guidelines in a large cohort of patients in the Netherlands

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Background: In 2003 a prospective cohort study of acute pancreatitis (AP) in the province of Northern Holland (2,2 million inhabitants) was initiated (EARL study). One of its aims is to investigate the clinical management of AP including nutritional interventions and adherence to guidelines. In these guidelines it is stressed that the time of starvation should be limited with early initiation of feeding ($\leq$ 5 days), preferably by the enteral route.
Methods: Patients were included from 18 hospitals. Hospital records and nursing reports were reviewed. Items regarding clinical and nutritional management were recorded in a study database. These included the length of hospital stay, severity of AP, the time period during which patients received no oral feeding; naso-enteric feeding with/without oral feeding, and TPN.
Results: Sufficient data was available from 111 hospital admissions of 93 patients. 82% (76/93) of patients had a first attack of AP and 17 patients had relapsing AP. The majority of patients suffered from edematous pancreatitis (93%) and were admitted on a gastroenterology ward (86% of admissions). Seven patients developed a necrotizing pancreatitis of whom 5 patients were admitted to a MCU/ICU. The overall median hospital stay was 11 (1-51) days. Patients admitted for more than 1 week had a median hospital stay of 14 (8-51) days. Nutritional interventions (including starvation) occurred in 96% (107/111) of the admissions. In 75% (80/107), the sole intervention was no oral feeding for a median period of 2 (1-12) days. In 23% (25/107) a no oral feeding regimen was combined with naso-enteral feeding. The median period of naso-enteral feeding (sole or in combination with oral feeding) was 8 (1-47) days and in 80% delivered the jejunal route. TPN was administered to 2 patients only for 5 and 21 days, respectively. The overall median period of starvation was 2 (0-12) days. In patients admitted more than 1 week, 12% (7/57) were starved for more than 5 days. In this subgroup the median percentage time of starvation was 43% (27%-60%) of the total hospitalization time.
Conclusions: The total time of starvation in patients with AP was limited in the majority of cases. Additional nutritional measures were undertaken reasonably quickly with enteral feeding via the jejunum as the preferred intervention. A small percentage of patients suffered from prolonged starvation which may potentially hamper recovery and outcome.

High-fat enteral feeding after hemorrhagic shock preserves gut wall integrity.

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In rats, the inflammatory response that arises after hemorrhagic shock is accompanied by loss of gut barrier function. Previously, in this model we have shown that high-fat enteral feeding activates the autonomic nerve system via release of cholecystokinin, leading to attenuation of the inflammatory response and maintenance of gut wall integrity via binding of achetylcholine on nicotinic receptors. This protective effect is established by high-fat enteral feeding before shock. However, in several clinical situations, shock is already present before treatment can be initiated. Therefore, the current study was designed to investigate whether high-fat feeding preserves gut barrier function after shock.
A model of nonlethal hemorrhagic shock was used in male Sprague Dawley rats in which 30-40% of blood volume was extracted. Subsequently, rats were either starved for 6 hours or received enteral high-fat nutrition, containing high amounts of phospholipids, or low-fat nutrition at 80, 180 and 360 minutes after hemorrhage. All rats were given standard chow ad libitum at 6 hours following shock and sacrificed at 24 hours after shock. Gut barrier function was assessed by measuring translocation of horseradish peroxidase (HRP) in ileal segments and bacterial translocation to mesenteric lymph nodes, liver and spleen. A Mann-Whitney U-test ($p<0.05$) was used for statistical analysis.
High-fat feeding significantly improved gut barrier function to HRP compared to animals that were starved (6.3 ± 0.8 vs. 8.9 ± 0.6 µg/ml; $p<0.05$). Translocation of HRP in the high-fat group was also reduced in comparison to the low-fat group (7.4 ± 1.0 µg/ml). Furthermore, bacterial translocation was significantly lower in high-fat fed animals compared to the starved group (34.1 ± 8.4 vs. 149.6 ± 35.4 CFU/g; $p<0.05$) and to the low-fat fed group (73.3 ± 16.1 CFU/g; $p<0.05$).

The effect of anti-oxidant enriched nutrition on oxidative stress after major upper gastro-intestinal tract surgery; a randomized clinical trial

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Major surgery and (subsequent) critical illness induce an immuno-inflammatory response, which is accompanied by production of reactive oxygen species (ROS) at the site of injury. The objective of this randomized, controlled study was to evaluate the effect of the intake of an additive mixture of nutrients with anti-oxidative properties (module AOX), on indicators of oxidative stress, in a group of patients undergoing major elective surgery of the upper gastro-intestinal tract. Included patients received enteral nutrition in the gut, with or without the supplementation of anti-oxidant nutrients during the week after surgery.21 patients were randomised after surgery to receive a standard enteral nutrition (Sondalis-ISO) (control group; n=11) versus an enteral nutrition enriched with glutamine, cysteine, zinc, selenium, α-tocopherol, β-carotene and vitamin C (treatment group; n=10) by jejunostomy. Observed parameters of oxidative stress were F2-isoprostane, malondialdehyde, glutathione and cyst(e)ine in the reduced and oxidized form and glutathione peroxidase. Also, indicators of the surgery-induced inflammatory response were determined. A GEE population-averaged model was used for statistical analysis, corrected for baseline values. $P<0.05$ was considered significant.Postoperative inflammation was reflected by an increase in CRP and IL-6. Levels of anti-oxidants were decreased on the first day after surgery in both groups. In the week after surgery levels of vitamin C and selenium increased significantly more in the treatment group. F2-isoprostane tended to decrease after the 5th day in the treatment group and the ratio GSH/GSSG was more enhanced during the first five days in the treatment group when compared with the control group. Interestingly, the anti-oxidant nutrition had a preservative effect on the gut, as levels of LBP decreased significantly faster in the treatment group after surgery.

Carbohydrate digestion and absorption in a rat model of cholestasis*

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Introduction: Cholestasis in children is frequently accompanied by an impaired nutritional status, which decreases the chances of long-term survival. We previously showed in a rat model of cholestasis that fat malabsorption importantly contributes to fecal energy loss (AJP 2000; 279:G1242-8). It is unclear, however, whether cholestasis also decreases the capacity to absorb other macronutrients *in vivo*, for example by interfering with small intestinal differentiation. We reasoned that absorption of carbohydrates could serve as a quantifiable marker for intestinal absorptive capacity during cholestasis.
Aim: To determine the effect of cholestasis on carbohydrate digestion and absorption in a rat model for obstructive cholestasis *in vivo*.
Methods: Male Wistar rats underwent bile duct ligation (cholestatic group) or sham operation (controls), (n=5-6 per group). Carbohydrate digestion and absorption were assessed by bolus administration of 1 mg ^{2}H-glucose and 0.25 g naturally enriched ^{13}C-sucrose via a duodenal catheter (ID), and subsequent determination of plasma ^{2}H-glucose and ^{13}C-glucose concentrations, resp. (mass spectrometry). Gene expression and enzyme activity of disaccharidases (sucrase-isomaltase and lactase) and gene expression of monosaccharide transporters (*Sglt1*, *Glut5* and *Glut2*) were quantified in duodenum, jejunum and ileum by RT-PCR and enzymatic assays, resp.
Results: Within 7.5 min after ID administration, plasma concentration of ^{2}H-glucose peaked to a similar extent in cholestatic and control rats (27 ± 15 and 24 ± 13 μmol/L, resp., NS). The plasma appearance of sucrose-derived ^{13}C-glucose was slower, with peak levels at 30 min, similarly in cholestatic and control rats (1.3 ± 1.6 and 2.0 ± 1.2 mmol/L, resp., NS). mRNA levels and enzyme activity of sucrase-isomaltase and lactase did not differ between cholestatic and control rats at any small intestinal segment, and neither did mRNA levels of the monosaccharide transporter genes *Sglt1*, *Glut5* or *Glut2*. Similar results were obtained in rats with bile diversion for 1 week (n=6), i.e. with similar intestinal bile deficiency but without cholestasis.
Conclusions: Intestinal deficiency of bile salts, with or without cholestasis, does not impair intestinal carbohydrate digestion or absorption in rats. These observations suggest that increasing the dietary carbohydrate intake can counteract a poor nutritional status induced by fat malabsorption in cholestatic children.

Gastric emptying of two carbohydrate-rich beverages, observed with scintigraphy

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A fasting period before surgery depletes the glycogen reserves. In combination with surgery this enhances postoperative insulin resistance, which is unfavorable for postoperative recovery. Preoperative intake of a specially designed carbohydrate-rich beverage (Nutricia PreOp®), was shown to attenuate postoperative insulin resistance and observed to pass the stomach within 2 hours. Recently, the preservation of the immune system after surgery was observed with the preoperative intake of Nutricia PreOp® (NP) and Roosvicee Vruchtenmix® (RV). RV was hypothesized also to be an effective beverage for preoperative use. The aim of the current study was to compare the gastric emptying of NP and RV. Eight volunteers participated in the study. Exclusion criteria were a precondition involving impaired gastric emptying and diabetes mellitus. Volunteers came to the hospital on two separate occasions in the morning, in post absorptive state. They were placed in front of a gamma camera and asked to drink NP or RV in randomized order, which contained an established amount of hepatate-Tc99m. Gastric emptying was observed in a sitting position during 2 hours. Venous, arterialized, blood was sampled, before and every 15 minutes after the intake of the beverage during observation, to measure the glucose and insulin response. The “area under the curve” was established for both beverages per volunteer to compare gastric emptying. Furthermore, tests for paired measurements (T-test or Wilcoxon) were applied ($p<0.05$ was considered significant). No differences were observed between the gastric emptying of NP and RV. After 2 hours the stomach was empty of NP in 5 volunteers and of RV in 3 volunteers. When compared to baseline, a significant increase was observed for glucose with both beverages during the first 60 minutes of gastric emptying. From 30 until 75 minutes the glucose response was significantly higher with NP, which reached a maximum value of 10 mmol/L as compared to 8 mmol/L with RV. The same trend was observed for the insulin response.
In conclusion, NP and RV pass the stomach in a comparable time-frame. In most volunteers, less than 20% of each beverage was present in the stomach after two hours of observation. The lower glucose and insulin response with RV suggest a more physiologic response and deserve further attention.

Defective Pathogen Recognition and Anti-Apoptotic Pathways in Dendritic Cells from NOD2 Mutant Crohn`s Disease Patients

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Mutations in the nucleotide-binding oligomerization domain 2 (NOD2) protein have been associated with the Crohn`s disease (CD) but the underlying mechanism is not completely understood. In order to study the pathogenetic mechanism NOD2-mediated CD, we analyzed the functional consequences of NOD2 mutations in patients-derived antigen-presenting cells. Monocyte-derived dendritic cells (DCs) from CD carriers of double-dose NOD2 mutations, wild type CD patients and wild type healthy volunteers were stimulated for 6 hours with NOD2 ligand muramyl dipeptide (MDP). Agilent Human Whole Genome Oligonucleotide arrays were used to assess the differential gene expression in the three studied groups. Significantly changed genes were analyzed by gene ontology mapping online software to identify differentially up-/down-regulated ontogenetic pathways. The most prominent pathway in the NOD2 mutant group, negative regulation of apoptosis, was functionally tested by CD40L induced apoptosis of MDP-primed DC from NOD2 mutant CD patients and wild-type healthy volunteers. Analysis of differentially expressed gene ontology pathways in the three studied groups showed an absence of transcription of pathogen response genes following NOD2 stimulation in the NOD2 mutant CD patients group. In addition, anti-apoptotic pathway was prominently up-regulated. This transcriptional activity of genes negatively regulating apoptosis was related to a significantly lower apoptosis rate and increased cell survival upon CD40L induction apoptosis in NOD2 mutant CD patients-derived DC compared with wild-type healthy volunteers.
Conclusion: Crohn`s disease related NOD2 variants lead to the disease development through induction of an ill-directed non-specific inflammatory reaction which is per-petuated by defective apoptosis of antigen-presenting cells.

Urease-induced calcium precipitation by bile-resistant Helicobacter species may initiate gallstone formation

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Background: Helicobacter species can colonize the gastrointestinal and hepatobiliary tract of many mammals, and often cause inflammation-associated diseases. Recently, infection with H. bilis and H. hepaticus has been linked to the formation of cholesterol gallstones in mice, but the mechanism underlying this phenomenon was not described. Gallstones are crystalline bodies formed by accretion or concretion of bile components. Bacteria that are able to colonize the harsh environment of the bile duct may initiate stone formation through calcium precipitation via the activity of the enzyme urease. In this study we have investigated whether Helicobacter species are bile resistant and their ability to initiate gallstone formation. Methods: A precipitation agar was developed which allowed for both the growth of Helicobacter species, and the testing of their ability to precipitate calcium. Bile acid-resistance was tested by growing H. hepaticus and H. pylori in media supplemented with a range of bile acids.
Results: Four urease-positive Helicobacter species (H. hepaticus, H. pylori, H. mustelae and H. bilis) were capable of precipitating calcium in our assay. In contrast, isogenic ureB urease-negative mutants of H. hepaticus, H. pylori and H. mustelae, and the urease-negative Helicobacter species H. cinaedi and H. pullorum were unable to do so. H. hepaticus was more resistant to deoxycholic acid and cholic acid than H. pylori, whereas their resistance to chenodeoxycholic acid did not differ.
Conclusion: Urease-positive Helicobacter species capable of colonizing the bile ducts may initiate the formation of gallstones via their urease activity. This provides a possible mechanism for the link between hepatobiliary colonization with urease-positive Helicobacter species and gallstone formation.

A high fat diet down-regulates gene expression of cholesterol efflux transporters in the small intestine of mice

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Metabolic syndrome is characterized by obesity, insulin resistance, hyperlipidemia and hypertension and is induced by chronic metabolic stress that can result from a disturbed balance between lipid metabolism and pro-inflammatory response. In the present study we investigated the effect of a high fat diet on gene expression of the cholesterol efflux transporters Abca1, Abcg5 and Abcg8 in the small intestine.C57BL/6 mice were fed a high (45 kcal% palmoil) or a low (10 kcal% palmoil) fat, cholesterol-free purified diet, for 2, 4 and 8 weeks. Intestinal RNA was isolated and gene expression patterns were analyzed using Affymetrix Mouse genome 430 2.0 microarrays. Data analysis showed that cholesterol efflux was down-regulated. Down-regulated transporters were Abca1, which transports cholesterol to ApoA1, and Abcg5 and Abcg8, which transport cholesterol back into the lumen. Furthermore several genes involved in cholesterol synthesis and chylomicron formation were up-regulated. Finally, Cyp27a1, which converts cholesterol into 27-hydroxycholesterol, an endogenous LXRα ligand, was down-regulated. These data indicate that the small intestine synthesizes endogenous cholesterol which is predominantly used for the chylomicron formation. As Abca1, Abcg5 and Abcg8 are LXRα target genes, we elucidated the role of LXRα in the down-regulation of these cholesterol efflux transporters. Therefore an intervention of 2 weeks with the same diets was performed with LXRα-/- mice. This study showed that the fat-induced down-regulation of cholesterol efflux transporters is not LXRα dependent.To investigate the acute fat responses, SV129 mice received via oral gavage 400 μl of C18:1, C18:2, C18:3, C20:5 and C22:6 in triglyceride form. After 6 hours the mice were sacrificed and gene expression was studied with qPCR. Also in this experiment, Abca1, Abcg5, Abcg8 and Cyp27a1 were down-regulated. Mttp was up-regulated, indicating that the chylomicron synthesis is already elevated.We conclude that fatty acids can down-regulate the small intestinal cholesterol efflux transporters Abca1, Abcg5 and Abcg8. This down-regulation is an acute response that remains consistent during long term diet intervention on a high fat diet and is not LXRα dependent. So, our data indicate that the enterocyte needs its endogenous cholesterol mainly for chylomicron formation to transport fat out of the cell, and therefore the cholesterol efflux via other pathways is reduced in an LXRα independent manner.

Altered intestinal motility in mice orally sensitized with cow's milk proteins

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Cow's milk allergy (CMA) is one of the leading causes of food allergy in children. Approximately 2.5% of infants exhibit CMA in Europe. Clinical features with IgE-mediated reactions are mostly expressed as immediate symptoms, which may involve the skin, respiratory tract, gastrointestinal tract and even sometimes an anaphylactic reaction. The pathogenesis of CMA involves a partial dysfunction in immunological tolerance during early life combined with enhanced intestinal permeability. Usually most patients outgrow their CMA by 3-5 years of age. However, IgE-mediated CMA predisposes the development of other (food) allergies and even asthma.
In order to assess aspects of prevention and treatment in the pathogenesis of cow's milk allergy our goal was to introduce a mouse model for orally induced cow's milk allergy.
3 Week old female C3H-HeOuJ mice were weekly orally sensitized with whey or casein using cholera toxin as adjuvant, for a period of 5 weeks (methods adapted from Li et al. and Frossard et al.). At week 6 the mice were challenged subcutaneously and orally. General markers like allergen specific IgE, IgG_1 and IgG_{2a} plasma levels and acute skin response (ear) were determined. Furthermore, functional intestinal responses were measured in the sensitized mice. Isotonic contractions of the ileum and colon were measured in order to get insight into motility changes of the gut. Permeability changes of the ileum were measured by means of Ussing chambers.
Antigen specific ear swelling was induced in whey and casein sensitized mice. Total IgE, whey specific IgE, IgG_1 and IgG_{2a} were significantly increased. For the casein sensitized mice this was less clear. Casein sensitized mice were found to have enhanced contractility of the ileum and reduced contractility of the colon after stimulation with carbachol (when compared with cholera toxin or PBS control mice). No motility changes were observed for whey sensitized mice. In the Ussing chamber a tendency towards increased permeability was observed in the casein sensitized mice.
The introduced mouse model to study orally induced cow's milk allergy, features an allergen specific acute allergic skin reaction and enhanced (specific) IgE, IgG_1 and IgG_{2a} plasma levels. Furthermore, intestinal motility changes were observed in casein sensitized mice. Functional changes within the intestine will be further elaborated in future studies.

Expression of matrilysin in gastrointestinal neoplasia infers a dualistic function

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Matrilysin (MMP-7) is a target gene of the canonical APC-Wnt pathway. Previous studies not only showed the presence of matrilysin in epithelial cells at the invasive front of colorectal and gastric cancers but implicated this proteinase also in more early stages of gastrointestinal neoplasia, e.g., Barrett's metaplasia, Helicobacter pylori infected gastric mucosa and colonic adenomas, indicating its significance for the whole tumorigenic process.We performed matrilysin immunohistochemistry on tumours derived from various tissues, including stomach, colon, breast and cervix. Besides staining of epithelial cells we found, for the first time, also matrilysin expression in endothelial cells, in particular in neo-angiogenetic areas of the tumors. CD34 co-staining confirmed the neo-angiogenetic origin of these endothelial cells. Although immunohistochemistry is a powerful and sensitive technique, it does not provide information on the functional activity of the proteinase. Therefore, we developed a specific immunocapture bioactivity assay (BIA) to determine active and total matrilysin levels, based on a matrix metalloproteinase sensitive amino-acid sequence in combination with a chromogenic peptide substrate and specific anti-matrilysin antibodies. Gastric and colorectal cancers were found to contain significantly increased levels of active and total matrilysin. Some cancer samples contained relatively little whereas others contained almost only active matrilysin compared to the total amount (active plus pro-form). Interestingly, also inflamed (H.pylori and ulcerative colitis) and adenomatous tissues were found to have highly increased matrilysin levels, but largely in the active form. Furthermore, in vitro experiments revealed human tumor cells and neo-angiogenetic endothelial cells to contain and secrete considerable amounts of matrilysin, similar to what was found in vivo.In conclusion, matrilysin is involved in gastrointestinal tumorigenesis, not only through neoplastic epithelial cells but also via the expression in neo-angiogenetic endothelial cells. Several important bioactive mediators have been shown to rely on matrilysin-mediated cleavage for their activity, indicating the impact of matrilysin in carcinogenesis. Further analyses of matrilysin and its and its activation in the integrated epithelial-endothelial network might have major implications for the understanding of invasion and angiogenesis in gastrointestinal carcinogenesis.

Prevalence of a second urease gene cluster in Helicobacter species colonising the carnivore stomach

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The enzyme urease is an essential virulence factor of *Helicobacter* species colonizing the gastric environment. The urease enzyme consists of UreA and UreB subunits, and is activated via the UreEFGH accessory proteins. All gastric *Helicobacter* species contain a *ureABIEFGH* gene cluster. Recently a gene cluster encoding a putative second urease (UreA2B2) was identified in *Helicobacter felis*. In this study we have investigated the prevalence of this second urease gene cluster in other *Helicobacter* species.
Southern hybridisation analysis was used to study the prevalence of ureB genes in gastric and enterohepatic *Helicobacter* species. Urease expression was monitored using immunoblotting. The *H. mustelae* genome sequence was obtained from the Sanger Institute Pathogen Sequencing Unit at http://www.sanger.ac.uk/Projects/H_mustelae.
Genomic DNA of *H. mustelae*, *H. felis* and *H. acinonychis* contained multiple restriction fragments hybridising to a *ureB*-specific probe, suggesting the presence of additional *ureB* genes. Expression of two UreB-like proteins was confirmed in *H. mustelae* and *H. acinonychis* using immunoblotting. Analysis of the *H. mustelae* and *H. acinonychis* genome sequences allowed identification of a gene cluster encoding UreA2 and UreB2 proteins. This gene cluster did not contain genes encoding urease accessory proteins. The *H. mustelae* and *H. acinonychis* UreB2 proteins are ~70% identical and ~90% homologous to the UreB proteins from the same species. Phylogenetically, *H. mustelae* and *H. acinonychis* UreB2 form a cluster together with *H. felis* UreB2, separately but close to *Helicobacter* UreB.
The urease-positive *Helicobacter* species *H. mustelae*, *H. acinonychis* and *H. felis* contain a gene cluster potentially encoding a second urease enzyme. Such a second urease gene cluster seems to be absent in *H. pylori* and enterohepatic *Helicobacter* species, and may only be present in *Helicobacter* species colonizing the stomach of carnivores. This suggests a link between diet and genetic properties of the colonizing *Helicobacter* species.

How Barrett's esophagus (BE) develops: the role of chronic inflammation in BE induction.

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Chronic inflammation probably plays an important role in the development of Barrett's esophagus (BE). However, little is known about the initial stages of BE development. In this study we aimed to determine the relationship between the genesis of intestinal metaplasia (IM) and the inflammatory response in the esophagus of rats during BE development. Esophagojejunostomy and gastrectomy (GEJ-model) was performed in 6 week old male Wistar rats (N=54). Rats were sacrificed at 0, 3, and 6 months. IM and inflammation were determined by histology and immunohistochemistry (IHC) in specimens of the esophagus.
At 3 months, no IM was observed by standard histology on H&E slides. However, markers for early IM formation, CDX2 and goblet cells, WE9, were already expressed in the deeper layers of the esophageal mucosa. In addition, an ulcerative inflammatory reaction, characterised by an influx of Th1 effector cells, such as monocytes, macrophages, and cytotoxic T cells was observed. At 6 months, all rats (21/21) had histologically complete IM with a mean length of 3.94 $\pm$ 1.48 mm, and IHC revealed strong CDX2 and goblet cell expression throughout the BE tissue. The number of inflammatory cells was 5-fold increased compared to month 3. The chronic nature of the inflammation was obvious by the influx of Th2 effector cells, such as B cells and IgG producing plasma cells. In addition, lymphoid aggregations were formed over time, which correlated in size with an increasing inflammatory response ($r=0.68$; $p<0.001$). Specifically in the area with BE, large lymphoid aggregations with a 50-fold increase in size were present, in which central proliferation was observed surrounded by a zone of B cells and a marginal T cell zone.
Conclusions: In our experimental rat model, formation of BE was observed over time. Moreover, early signs of BE, characterized by specific markers for IM and goblet cells, were already seen before histological IM was present. Based on our findings, it can be concluded that the induction of BE starts with a Th1 derived inflammatory reaction, which shifts towards a chronic Th2 response, characterized by plasma cells and the formation of lymphoid aggregations. This model can be used to investigate whether BE induction can be delayed or even prevented by treatments that inhibit the shift towards a Th2 response in the esophagus.

Putative role for immunoglobulin-free light chain in inflammatory bowel disease and irritable bowel syndrome

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Nowadays it is widely recognized that mast cells are involved in non-allergic (non-IgE) chronic diseases. Inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS) are interrelated intestinal disorders both related with increased numbers of mast cells and mast cell activation in the gastro-intestinal tract. The recent finding that immunoglobulin-free light chains (IgLC) can induce hypersensitivity-like responses, suggests that IgLC may be of import in the pathophysiology of mast cell-associated diseases such as inflammatory bowel diseases (IBD). In the mouse, a colonic hypersensitivity reaction, induced by skin sensitization with dinitrofluorobenzene (DNFB) followed by an intra-rectal application of the hapten, features as a mast cell-dependent model for IBD. Using this model, we now have shown that the IgLC-antagonist, a 9-mer peptide F991, can abrogate the development of diarrhea, cellular infiltration and colonic lymphoid follicle hyperplasia. In addition, a decline in mouse mast cell protease 1 (mMCP-1) in serum was found indicating that F991 inhibits DNFB-induced mast cell activation. Furthermore, passive immunization with antigen-specific IgLC and subsequent rectal hapten challenge elicited local mast cell activation and increases in vascular permeability in the colon of mice. First indication of clinical relevance for IgLC is demonstrated by increased serum levels of IgLC in IBD and IBS patients. Furthermore, IgLC is shown to be present in the intestinal mucosa and inflammatory lesions in biopsies of IBD patients associated with the presence of plasma cells and mast cells. Our findings may provide new insights into the pathogenesis of IBD and IBS. In addition, the ability to inhibit IgLC function pharmacologically provides a novel therapeutic means to prevent or ameliorate the adverse gastrointestinal manifestations of IBD and IBS.

5-Aminosalicylic acid interferes with cell cycle progression of colorectal cancer cells

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We reported earlier on the ability of 5-aminosalicylic acid (5-ASA) to reduce the cell growth of the colorectal cancer cells, HT29, Caco2 and Colo205. We now aimed to unravel the mechanisms behind this cell growth reduction. Flow cytometry analysis, including cyclin A/B1 and phospho-histone H3 (a marker of chromosomal condensation), showed that 5-ASA induced cell cycle arrest in the G2/M phase of HT29 cells. Microscopic analysis confirmed that these cells are arrested in mitosis. An arrest in S-phase was also found depending on the dosage used. Aberrant mitotic spindles, leading to features of mitotic catastrophe, i.e., giant cells containing multiple micronuclei, were also found. In contrast to HT29 cells, Caco2 cells were arrested in the G0/G1 phase. In both cell lines a dose-dependent increase in apoptosis by 5-ASA was also found, as assessed by Annexin V flow cytometry and immunohistochemical detection of a caspase-cleavage product of cytokeratin 18 (M30), in addition to the classical morphological features of apoptosis. The secretion of intact cytokeratin 18 in the medium of the cells, besides the M30 cleavage product, also suggests the induction of necrosis. 5-ASA's anti-inflammatory actions have been reported to be dependent on activation of the peroxisome proliferation activated receptor gamma (PPARγ). GW9662, a specific PPARγ antagonist, was not able to antagonize 5-ASA's effects on cell proliferation, indicating that its growth inhibitory effects are PPARγ independent. Thus, our experiments indicate that 5-ASA interferes in the cell cycle progression of colorectal cancer cells *in vitro* and induces (regulated) cell death. These responses are time-, concentration-, dosage- and cell-type-dependent and PPARγ independent, and partly explain 5-ASA's chemo-preventive properties.

ALFABETISCHE LIJST VAN STANDHOUDERS NAJAARSCONGRES 2006

B = Beneluxhal
K = Kempenhal

naam	Standnr.
Abbott B.V.	K 18
ALTANA Pharma B.V.	B 26
ALTANA Pharma B.V. Asacol	B 5
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Danica Nederland B.V.	K 9
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Endomed B.V.	B 25
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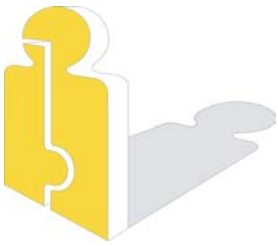
Plattegrond expositie

AANMELDINGSFORMULIER VOOR HET LIDMAATSCHAP VAN DE NEDERLANDSE VERENIGING VOOR GASTROENTEROLOGIE



Naam : M/V*
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Geboortedatum :
Titel :
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instituut :
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Doctoraalexamen : ja/neen*; zo ja, welke studierichting:
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o Sectie Neurogastroenterologie en Motiliteit
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o Sectie Kindergastroenterologie
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Nederlandse Vereniging voor Hepatologie

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SEVA Sectie endoscopie verpleegkundigen en assistenten

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Instituut :
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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.*

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