# Programma voorjaarsvergadering 22 en 23 maart 2007

**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 tijdens voorjaarsvergadering:***

| | |
|---|---|
| *Assistentenvereniging Touché (mdl-artsen i.o.)* | *22 maart, 12.30 uur - Zaal 82/83* |
| *Nederlandse Vereniging voor Hepatologie* | *22 maart, 15.00 uur - Parkzaal* |
| *Nederlandse Vereniging voor Gastroenterologie* | *22 maart, 21.00 uur - Brabantzaal* |

**INHOUDSOPGAVE** pag.

## VRIJDAG 23 MAART 2007

### Ochtendprogramma



### Middagprogramma



***Tijdstippen diverse ledenvergaderingen tijdens voorjaarsvergadering:***

| | |
|---|---|
| *Sectie Endoscopie Verpleegk. en Assistenten* | *23 maart, 11.30 uur - Diezezaal* |
| *Sectie Experimentele Gastroenterologie* | *23 maart, 12.00 uur - Auditorium* |
| *Nederlands Genootschap van MDL-artsen* | *23 maart, 12.00 uur - Zaal 80-82* |

## VOORWOORD

Hierbij treft u het volledige programma aan van de voorjaarsvergadering van de Nederlandse Vereniging voor Gastroenterologie op 22 en 23 maart 2007 in Congrescentrum Koningshof te Veldhoven.

Het programma zal donderdag 22 maart om 13.00 uur van start gaan met een aantal vrije voordrachten van de NVGE, de Sectie Neurogastroenterologie en Motiliteit en de Nederlandse Vereniging voor Gastrointestinale Chirurgie. In de middag zijn er twee symposia: het IBD symposium getiteld "Topics uit de Nederlandse IBD-richtlijn" en van de Nederlandse Vereniging voor Hepatologie een klinisch symposium getiteld: "New developments in Hepatobiliary Disease'. Daarnaast is er een sessie met vrije voordrachten van the Netherlands Society of Parenteral and Enteral Nutrition. Om 17.00 uur vindt in de Brabantzaal de toekenning plaats van het NVGE erelidmaatschap aan prof. dr. G.P. van Berge Henegouwen en prof. dr. P.B. Soeters. Alle leden worden van harte uitgenodigd hierbij aanwezig te zijn! Na het diner vindt in de Brabantzaal de Presidential Selection plaats. Deze plenaire avondsessie begint om 20.00 uur.

Op vrijdag 23 maart is er in de ochtend het Lustrumsymposium van de Sectie Experimentele Gastroenterologie getiteld: "Celebrate 10 years of Basic Research on Gastrointestinal Disease, future perspectives". Dit symposium vindt plaats in het Auditorium.
De Sectie Gastrointestinale Endoscopie verzorgt in de Brabantzaal een tweetal voordrachten over nieuwe technieken in ERCP, gevolgd door vrije voordrachten in het tweede deel van de ochtend. Gedurende de rest van de dag zijn er veel sessies met vrije voordrachten van de Nederlandse Vereniging van Gastroenterologie, de Sectie Experimentele Gastroenterologie en de Nederlandse Vereniging voor Hepatologie. Ook zullen er een aantal MLDS-projecten gepresenteerd worden. In respectievelijk de Diezezaal en de Parkzaal worden tot slot door de Sectie Endoscopie Assistenten en Verpleegkundigen en de Vereniging van Maag Darm Lever Verpleegkundigen eigen programma's met lezingen verzorgd.

**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 PowerPoint presentatie tevoren controleren.

Graag tot ziens in Veldhoven!

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

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

# Belangrijke mededeling

**over de aanwezigheid van farmaceutische industrieën**

*Aan alle deelnemers aan de voorjaarsvergadering*

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

## Cursorisch onderwijs in maag-darm-leverziekten, 21 en 22 maart — Auditorium

**Cursuscommissie:**
Dr. C.J.H.M. van Laarhoven, (chirurg, Elisabeth Ziekenhuis Tilburg)
Dr. H.M. van Dullemen (MDL-arts, UMC Groningen)
Drs. S.V.A. Jarbandhan (MDL-arts i.o, VU medisch centrum)
Dr. R.A. de Man (MDL-arts, Erasmus MC)
Prof. dr. C.J.J. Mulder (MDL-arts, VU medisch centrum)
Dr. A.M.P. de Schryver (MDL-arts i.o., UMC Utrecht

**Woensdag**
**21 maart 2007** *Dunne darm*

20.00 – 20.50 Short Bowel Syndroom, wat gaat erin, wat gaat eruit?
*Dr. G. Dijkstra, maag-darm-leverarts, UMCG*

21.00 – 21.20 Anorexia nervosa, een nieuwe manier van denken.
*Drs. A.A. van Elburg, jeugdpsychiater, UMCU*

21.30 – 22.00 PEG-PEJ-TPV, bij wie, wanneer, wat?
*Dr. G.J.A. Wanten, maag-darm-leverarts, UMCN*

22.10 – 22.30 Prevalentie ondervoeding, hoe meten we, prestatie-indicator?
*Mw. M. Nieboer, Diëtetiek, Maxima Medisch Centrum, Eindhoven*

**Donderdag**
**22 maart 2007** *Dunne darm / Pancreas*

08.00 – 08.20 Voeding tot in de OK, bij wie, wat, hoeveel?
*Prof. dr. R.P. Bleichrodt, chirurg, UMCN*

08.30 – 08.50 Imaging dunne darm: MRI, VCE, DBE, plaatsbepaling
*Dr. M.A.J.M. Jacobs, maag-darm-leverarts, VUmc*

09.00 – 09.20 MRI-CT pancreas
*Dr. O.M. van Delden, radioloog, AMC*

09.30 – 09.50 Pijnbestrijding pancreas
*Prof. dr. J.B.M.J. Jansen, maag-darm-leverarts, UMCN*

*pauze*

10.30 – 10.50 Genetica van chronische pancreatitis
*Prof. dr. J.P.H. Drenth, maag-darm-leverarts, UMCN*

11.00 – 11.20 Exocriene pancreasinsufficiëntie, diagnostiek en therapeutische strategie
*Dr. M.J. Bruno, maag-darm-leverarts, AMC*

11.30 – 11.50 Management of acute and chronic panreatitis. Do we change?
*Dr. J. Kleeff, Heelkunde, Heidelberg*

12.00 – 12.30 Pancreatitis: blik in de toekomst van een chirurg
*Prof. dr. H.G. Gooszen, chirurg, UMCU*

*De cursuscommissie verwacht van MDL-artsen i.o. dat ze de Cursus Klinische Hepatologie (NVH) éénmaal bezoeken in het tweede deel van de MDL-opleiding (jaar vier tot zes).*

# Programma donderdag 22 maart 2007

| DONDERDAG | BRABANTZAAL | BARONIEZAAL | PARKZAAL | AUDITORIUM | DIEZEZAAL |
|---|---|---|---|---|---|
| 13.00-15.00 | Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie<br><br>p. 10 | Vrije Voordrachten Sectie Neurogastroenterologie en Motiliteit<br><br>p. 14 | Vrije voordrachten Nederlandse Vereniging voor Gastrointestinale Chirurgie<br><br>p. 18 | Geen programma in deze zaal op donderdagmiddag | Geen programma in deze zaal op de donderdag |
| 15.00-15.30 | Theepauze | Theepauze | Thee / ledenvergadering | | |
| 15.30-17.00 | **Topics uit de Nederlandse IBD-richtlijn**<br><br>p.12 | Vrije voordrachten Netherlands Society of Parenteral and Enteral Nutrition<br><br>p. 16 | **Symposium NVH**<br>'**New developments in Hepatobiliary Disease'**<br><br>p. 20 | Geen programma in deze zaal op donderdagmiddag | |
| 17.00 | **Uitreiking erelidmaatschap** aan Prof. dr. G.P. van Berge Henegouwen en Prof. dr. P.B. Soeters p. 13 | Geen parallelle sessie | **Vervolg Symposium NVH**<br>'New developments in Hepatobiliary Disease' | | |
| 17.30 | Congresborrel en diner | | | | |
| 20.00 | **Presidential Selection**<br>p. 22 | | | | |
| 21.00 | **Ledenvergadering NVGE** | | | | |

# Programma vrijdag 23 maart 2007

| VRIJDAG | BRABANTZAAL | BARONIEZAAL | PARKZAAL | AUDITORIUM | DIEZEZAAL |
|---|---|---|---|---|---|
| 08.30<br><br>09.00 | **Casuïstiek voor de clinicus**<br><br>**Nieuwe technieken in ERCP**<br>Gevolgd door vrije voordrachten<br><br>p. 24 | Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie<br><br>p. 27 | Programma van Vereniging voor Maag-Darm-Lever Verpleegkundigen<br><br>p. 41 | Vrije voordrachten SEG<br>**09.00: Lustrumsymposium Sectie Experimentele Gastroenterologie**<br>'Celebrate 10 years of Basic Research on Gastro-intestinal Disease, future perspectives' p. 32 | Programma van Sectie Endoscopie Verpleegkundigen en Assistenten<br><br>p 40 |
| 10.00 | Koffiepauze, expositie | Koffiepauze, expositie | Koffiepauze, expositie | Koffiepauze, expositie | Koffiepauze, expositie |
| 10.30 | Vrije voordrachten Sectie Gastrointestinale Endoscopie<br><br>p. 24 | Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie<br><br>p. 29 | Programma van Vereniging voor Maag-Darm-Lever Verpleegkundigen<br><br>p. 41 | Vervolg Lustrumsymposium Sectie Experimentele Gastroenterologie<br><br>p. 32 | Programma Sectie Endoscopie Verpleegkundigen en Assistenten<br><br>p. 40 |
| 12.00 | Lunch expositiehal | Lunch expositiehal | Lunch + ledenverg. SEG | Lunch expositiehal | Lunch expositiehal |
| 13.30 | Presentaties MLDS projecten en vrije voordrachten Sectie Experimentele Gastroenterologie<br><br>p. 34 | Vrije voordrachten Nederlandse Vereniging voor Hepatologie<br><br>p. 36 | Programma van Vereniging voor Maag-Darm-Lever Verpleegkundigen<br><br>p. 41 | Vrije voordrachten Sectie Experimentele Gastroenterologie<br><br>p. 38 | Pprogramma Sectie Endoscopie Verpleeg-kundigen en Assistenten<br><br>p. 40 |
| 15.00 | Einde programma, thee | Einde programma, thee | Einde programma, thee | Einde programma, thee | Einde programma, thee |

**Nederlandse Vereniging voor Gastroenterologie** **Brabantzaal**

12.30 Inschrijving, koffie

**Voorzitter:** A.A. van Bodegraven en P.C.F. Stokkers

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

13.00 The influence of active smoking, passive smoking and smoking cessation on the disease course and behaviour of inflammatory bowel disease (p.42)
*F. van der Heide[1], A. Dijkstra[2], R.K. Weersma[1], F. Albersnagel[3], W.J. Sluiter[4], J.H.Kleibeuker[1] and G. Dijkstra[1]. Depts of Gastroenterology[1], Social and Organizational Psychology[2], Health Psychology[3], and Endocrinology[4]. University Medical Center Groningen, The Netherlands*

13.10 Faecal calprotectin: a non-invasive marker of disease activity in Inflammatory Bowel Disease (p. 43)
*R.P.H. Bokkers[1,3], F.A.J.T.M. van den Bergh[2], J.J. Kolkman[1], M.G.V.M. Russel[1]. Depts. of Gastroenterology[1] and Clinical Chemistry[2], Medical Spectrum Twente, and Radiology[3], University Medical Centre Utrecht, Utrecht, The Netherlands*

13.20 Sodium and liquid balance in ileostomy subjects (p. 44)
*C.A. Bouwman[1], M. Regelink[2], L. van Nispen[2], E. Siebelink[2], A.H.J. Naber[1,3]. Dept of Gastroenterology and Hepatology[1], Radboud University Nijmegen Medical Centre, Div. of Human Nutrition[2], Wageningen University, Dept of Internal Medicine[3], Ter Gooi Hospitals, The Netherlands*

13.30 Predictive factors of response to cyclosporine and quality-of-life in steroid-refractory ulcerative colitis. A long term follow-up (p. 45)
*H. Blokzijl[1], A.B.U. Mäkelburg[1], F.G.A. Jansman[2], A.C. Poen[1], B.D. Westerveld[1], J. Vecht[1]. Depts of Gastroenterology and Hepatology[1], and Clinical Pharmacology[2], Isala klinieken, Zwolle, The Netherlands*

13.40 Infliximab in paediatric Crohn's disease: long-term follow-up of an unselected cohort* (p.46)
*L. de Ridder[1], E.H. Rings[2], M.A. Benninga[3], J.A.J.M. Taminiau[3], C.M.F. Kneepkens[1], J.C. Escher[41]. VU Medical Center, Amsterdam[2], University of Groningen/Beatrix Children's Hospital, Groningen[3], Emma Children's Hospital, Amsterdam[4], Sophia Children's Hospital, Rotterdam, The Netherlands*

13.50 Natalizumab does not require the concomitant use of immunosuppressants or corticosteroids for the induction of sustained response and remission (p. 47) *S. van Deventer[1], B. Feagan[2], R. Fedorak[3], R. Panaccione[4], D. Present[5], P. Rutgeerts[6], W. Sandborn[7], M. Spehlmann[8], Z. Tulassay[9], M. Volfova[10], D. Wolf[11], S. Targan[12]. Academic Medical Centre[1], Amsterdam, The Netherlands, Roberts Research Institute[2], University of Western Ontario, London, University of Alberta[3], Edmonton, University of Calgary[4], Calgary, Canada, Mount Sinai Hospital[5], New York, Mayo Clinic[7], Rochester, Atlanta Gastroenterology Associates[11], Atlanta, Cedars Sinai[12], Los Angeles, United States, Gasthuisberg[6], Leuven, Belgium, Asklepsios Westklinikum[8], Hamburg, Germany, Semmelweis University[9], Budapest, Hungary, Hepato-Gastroenterology[10], Hradec Králové, Czech Republic*

14.00 A single centre experience of adalimumab treatment in patients with luminal and fistulizing Crohn's disease (CD): do antibodies to infliximab (ATIs) affect clinical outcome? (p. 48)
*R.L. West[1], E.J. Kuipers[1], P. van der Toorn[1], E.H.C.J. Buster[1], P.B.F. Mensink[1], G.J. Wolbink[2], C.J. van der Woude[1]. Erasmus Medical Centre, Rotterdam, The Netherlands*

14.10 Prenatal exposure to famine and functional bowel disorders (p. 49)
*T.K.Klooker[1], B. Braak[1], R.C. Painter[2], S.R. de Rooij[2], R.van Elburg[3], R.M. van den Wijngaard[1], G.E. Boeckxstaens[1], T.J. Roseboom[2], Academic Medical Centre, Amsterdam, The Netherlands*

14.20 Additional use of enemas versus conventional treatment in children with severe constipation: a randomized controlled trial* (p. 50)
*M.E.J. Bongers, M.M. van den Berg, W.P. Voskuijl, M.A. Benninga. Dept of Pediatric Gastroenterology and Nutrition, Academic Medical Centre, Amsterdam, The Netherlands*

14.30 Enhanced expression of genes associated with visceral hypersensitivity in the small intestine of Irritable Bowel Syndrome patients (p. 51)
*A.P.M. Kerckhoffs[1], J.J.M. ter Linde[1], L.M.A. Akkermans[2], M. Samsom[1], Gastrointestinal Research Unit, Depts of Gastroenterology[1], and Surgery[2], University Medical Centre Utrecht, Utrecht, The Netherlands*

14.40 The mode of delivery in females with Crohn's disease (p. 52)
*M. Smink[1], L. Albers[1,2], Z. Nawabi[1,2], F.K. Lotgering[1], D.J. de Jong[2].*
*Depts of Gynaecology and Obstetry[1], Gastroenterology and Hepatology[2]. Radboud University Nijmegen Medical Center, The Netherlands*

*Donderdag 22 maart 2007*

14.50 Carcinogenesis in Peutz-Jeghers syndrome (p. 53 + 54)
(MLDS project no. MWO 01-03)
*W.W.J. de Leng, H. Van Dekken, A.F.P.M. de Goeij, J.J. Keller, F.W.M. de Rooij, M.A.J. Weterman, F.M. Giardiello, J.H.P. Wilson, G.J.A. Offerhaus*
*Dept of Pathology, University Medical Center Utrecht, Utrecht*

15.00 Einde vrije voordrachten, theepauze

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**IBD-symposium** **Brabantzaal**

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**Voorzitter**: A.A. van Bodegraven namens de Initiative on Crohn and Colitis (ICC)

**Topics uit de Nederlandse IBD richtlijn**

15.30 Richtlijn ontwikkeling CBO en ECCO
*Dr. D.J. de Jong, MDL-arts in UMC St. Radboud*

15.40 Biologicals in behandeling van IBD
*Dr. G. Dijkstra, MDL-arts in UMC Groningen*

16.10 Chirurgie bij IBD
*Spreker ten tijde van het drukken van dit boekje nog niet definitief*

16.20 IBD op de kinderleeftijd
*Dr. J.C. Escher, kinderarts Erasmus MC*

16.40 Plenaire discussie: complexe IBD

17.00 Einde programma

## Nederlandse Vereniging voor Gastroenterologie — Brabantzaal

**Voorzitter:** J.B.M.J. Jansen

17.00 Toekenning van het erelidmaatschap van de Nederlandse Vereniging voor Gastroenterologie aan Prof. dr. G.P. van Berge Henegouwen en Prof. dr. P.B. Soeters.

17.30 Congresborrel

18.00 Diner in de Genderzaal

## Sectie Neurogastroenterologie en Motiliteit — Baroniezaal

**Voorzitter:** M.A. Benninga en J.W. Straathof

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

13.00 Effect of sildenafil on gastric function assessed with Magnetic Resonance Imaging (p. 55)
*N.P.M. Paridaans[2], J.J.L. Haans[1,2], P.H.C. Eilers[4], J. Doornbos[3], A. de Roos[3], A.A.M. Masclee[1]. Dept of Gastroenterology and Hepatology[1], University Hospital Maastricht, Maastricht, Depts of Gastroenterology and Hepatology[2], Radiology[3], and Medical Statistics[4], Leiden University Medical Center, Leiden, The Netherlands*

13.10 The role of proximal gastric volume in spatial separation of diaphragm and lower esophageal sphincter in GERD patients and controls (p. 56)
*R.C.H. Scheffer[1], A.J. Bredenoord[1], H.G. Gooszen[2], G.S. Hebbard[3], M. Samsom[2,1]. Dept of Gastroenterology, St. Antonius Hospital, Nieuwegein, Gastrointestinal Research Unit, Depts of Gastroenterology and Surgery[2], University Medical Center Utrecht, The Netherlands, Dept of Gastroenterology[3], The Royal Melbourne Hospital, Australia*

*Donderdag 22 maart 2007*

13.20 Central activation of the cholinergic anti-inflammatory pathway reduces postoperative ileus in mice (p. 57)
*F.O. The[1], J. van der Vliet[2], W.J. de Jonge[1], R.J. Bennink[3], R.M. Buijs[2], G.E. Boeckxstaens[1]. Dept of Gastroenterology and Hepatology[1], Netherlands Institute for Neuroscience[2], Dept of Nuclear Medicine[3], Amsterdam, The Netherlands*

13.30 Predicting factors for repeated pneumatic balloon dilatation in patients with primary achalasie (p. 58)
*J. Alderliesten, J.M. Conchillo, I. Leeuwenburgh, E.J. Kuipers. Dept of Gastroenterology and Hepatology, Erasmus MC, University Medical Center Rotterdam, The Netherlands*

13.40 Involvement of TRPV1 in visceral hypersensitivity to distension in the rat (p. 59)
*R.M. van den Wijngaard, O. Welting, W.J. de Jonge, G.E. Boeckxstaens. Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands*

13.50 Safety and Efficacy of Tegaserod in Children* (p. 60)
*O. Liem[1], H.M. Mousa[2], M.A. Benninga[1], C. Di Lorenzo[2]. Dept of Pediatric Gastroenterology and Nutrition[1], Emma Children's Hospital, Academic Medical Center, Amsterdam, The Netherlands, Division of Pediatric Gastroenterology[2], Columbus Children's Hospital, Columbus, Ohio, USA*

14.00 Mast cell stabilization as treatment of post-operative ileus: a clinical proof of principle study (p. 61)
*F.O. The[1], M.R. Buist[2], A. Lei[1], R.J. Bennink[3], J. Hofland[4], R.M. van den Wijngaard[1], W.J. de Jonge[1], G.E. Boeckxstaens[1]. Depts of Gastroenterology and Hepatology[1], Obstetrics and Gynaecology[2], Nuclear Medicine[3], and Anaesthesiology[4], Academic Medical Center, Amsterdam, The Netherlands*

14.10 Serotonin receptor 3A polymorphism C178T is associated with visceral hyper- sensitivity in GERD patients (p. 62)
*D.R. de Vries, J.J.M. Ter Linde, M.A. van Herwaarden, A.J.P.M. Smout, M. Samsom. Dept of Gastroenterology, University Medical Center Utrecht, The Netherlands*

14.20 Localized distension of the esophagogastric junction augments triggering of TLESRs in healthy volunteers: A novel neuroregulatory mechanism* (p. 63)
*M.P. van Wijk[1,2], M.A. Benninga[1], G.P. Davidson[2], T.I. Omari[2]. Dept of Paediatric Gastroenterology & Nutrition[1], Emma Children's Hospital/AMC, Amsterdam, The Netherlands, Centre for Paediatric and Adolescent Gastroenterology[2], Women's and Children's Hospital, Children's Youth and Women's Health Services, Adelaide, Australia*

14.30 The gastroesophageal pressure gradient in GERD, relationships with obesity and hiatal hernia (p. 64)
*D.R. de Vries, M.A. van Herwaarden, A.J.P.M. Smout, M. Samsom. Dept of Gastroenterology, University Medical Center Utrecht, The Netherlands*

14.40 Fundoplication reduces gastroesophageal reflux in a refluxate-dependent manner (p. 65)
*A.J. Bredenoord[1], W.A. Draaisma[2], B.L.A.M. Weusten[1], H.G. Gooszen[2], A.J.P.M. Smout[3]. Dept of Gastroenterology[1], St Antonius Hospital Nieuwegein, Dept of Surgery[2], and Gastrointestinal Research Unit[3], University Medical Center Utrecht, The Netherlands*

14.50 Neuroregulation of the TLESR reflex by sensory mechanisms sensitive to luminal contents at the esophago-gastric junction: A study in neonates with adult implications* (p. 66)
*M.P. van Wijk[1,2], M.A. Benninga[1], J. Dent[3], R. Lontis[4], L. Goodchild[4], R. Haslam[4], G.P. Davidson[2], T.I. Omari[2]. Dept of Paediatric Gastroenterology and Nutrition[1], Emma Children's Hospital/AMC, Amsterdam, The Netherlands, CPAG[2], Women's and Children's Hospital, CYWHS, Adelaide, Australia, Dept of Gastroenterology[3], RAH, Adelaide, Australia, Dept of Neonatal Medicine[4], CYWHS, Adelaide, Australia*

15.00 Theepauze

**Netherlands Society of Parenteral and Enteral Nutrition** **Baroniezaal**

**Voorzitters:** G. Wanten en C.H.C. Dejong

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

15.30 Butyrate modulates oxidative stress in the colonic mucosa of healthy humans (p. 67)
*H.M. Hamer[1,2], D. Jonkers[1,2], F. Troost[1,2], A. Bast[3], S. Vanhoutvin[1,2], K. Venema[1,4], R-J. Brummer[1,2]. Wageningen Centre for Food Sciences[1], Wageningen, Div. of Gastroenterology-Hepatology[2], and Dept of Pharmacology and Toxicology[3], NUTRIM, Maastricht University, Maastricht, TNO[4], Quality of Life, Zeist, The Netherlands*

15.40 Enteral nutrition reduces the risk of mortality and infectious complications in patients with predicted severe acute pancreatitis: a meta-analysis comparing enteral and parenteral nutrition (p. 68)
*H.C. van Santvoort[1], M.G. Besselink[1], M.S. Petrov[1], G.J.M.G. van der Heijden[2], J.A. Windsor[3], H.G. Gooszen[1]. Dept of Surgery[1], Julius Center for Health Sciences and Primary Care[2], University Medical Center Utrecht, The Netherlands, Dept of Surgery[3], University of Auckland, New Zealand*

15.50 High-fat enteral nutrition reduces hepatic damage following combined exposure to bacterial DNA and hemorrhagic shock (p. 69)
*M.D.P. Luyer, J. Derikx, M. Hadfoune, J.J. de Haan, T. Lubbers, C.H.C. Dejong, E. Heineman, W.A. Buurman, J.W.M. Greve. Dept of surgery, Academic Medical Hospital Maastricht, The Netherlands*

16.00 Formula feeding leads to decreased gut barrier function and an excessive systemic inflammatory response to luminal bacterial endotoxin (p. 70)
*M. Schellart[1], G. Thuijls[1], M. Koeneman[1], C.L.G.J. Smeets[1], C. Steele[2], E. Heineman[1], W.A. Buurman[1]. Dept of Surgery, University Hospital Maastricht[1], The Netherlands, Dept of Pediatrics[2], Children's Hospital in Pittsburgh, PA*

16.10 Comparison of ileal and duodenal brake mechanisms on satiety and gastrointestinal transport (p. 71)
*J. Maljaars[1], E.A. Haddeman[2], H.P.F. Peters[2], A.A.M. Masclee[1]. Dept of Gastroenterology and Hepatology[1], University Hospital Maastricht, Maastricht, Energy, Weight Control & Performance Skillbase[2], Unilever Food & Health Research Institute, Vlaardingen, The Netherlands*

16.20 Evidence for modulation of leukocyte count but not neutrophil activation in healthy humans after intravenous administration of long- and medium-chain-based parenteral lipid emulsions (p. 72)
*M.W. Versleijen[1], H. Roelofs[1], S.E. van Emst-de Vries[2], P.H. Willems[2], G.J. Wanten[1]. Depts of Gastroenterology and Hepatology[1], and Biochemistry[2], University Medical Center Nijmegen, The Netherlands*

16.30 A critical appraisal of clinical practices regarding endoscopically placed nasojejunal-feeding tubes: a prospective single-center study (p. 73)
*G. Bouman[1], T. van Achterberg[2], G. Wanten[1]. Dept of Gastroenterology and Hepatology[1] and Centre for Quality of Care Research[2], Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands*

16.40 Does the route of administration (enteral or parenteral) of isotopically labelled L-glutamine affect the conversion of L-[2-15N]glutamine into L-[2-15N]arginine in humans (p. 74)
*G.C. Ligthart-Melis[1], M.C.G. van de Poll[2], C.H.C. Dejong[2], P.G. Boelens[1], N.E.P. Deutz[2], P.A.M. van Leeuwen[1]. VU University Medical Centre[1], Amsterdam, Nutrition and Toxicology Research Institute Maastricht[2] (NUTRIM), University Hospital Maastricht, The Netherlands*

16.50 Faecal weight to diagnose malabsorption at the Intensive Care Unit (p. 75)
*N.J. Wierdsma[1], A.A. van Bodegraven[2], R.J.M. Strack van Schijndel[3]. Depts of Nutrition and Dietetics[1], Gastroenterology-Small bowel unit[2], Intensive Care Unit[3], VU University Medical Centre, Amsterdam, The Netherlands*

17.00 Einde vrije voordrachten

Voor het bijwonen van de toekenning van het erelidmaatschap van de Nederlandse Vereniging voor Gastroenterologie aan Prof. dr. G.P. van Berge Henegouwen en Prof. dr. P.B. Soeters kunt u zich begeven naar de Brabantzaal.

## Nederlandse Vereniging voor Gastrointestinale Chirurgie — Parkzaal

**Voorzitter:** C.J.H. van Laarhoven en J. Stoot

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

13.00 Development of a nomogram to predict complications after esophagectomy for cancer (p. 76)
*S.M. Lagarde[1], J.B. Reitsma[2], A.K.D. Maris[1], A.H. Zwinderman[2], M.I. van Berge Henegouwen[1], O.R.C. Busch[1], J.J.B. van Lanschot[1]. Depts of Surgery[1], and Clinical Epide-miology and Biostatistics[2], Academic Medical Center, University of Amsterdam, The Netherlands*

13.10 Nurse-led follow-up of patients after esophageal cancer surgery: a randomized trial (p. 77)
(MLDS-project no. SWO 02-04)
*E.M.L. Verschuur[1], M-L. Essink-Bot[2], E.J. Kuipers[1], S. Polinder[2], T.C.K. Tran[3], A. van der Gaast[4], L.P.S. Stassen[5], H.W. Tilanus[3], E.W. Steyerberg[2], P.D. Siersema[1]. Depts of Gastroenterology & Hepatology[1], Public Health[2], Surgery[3], and Medical Oncology[4], Erasmus MC, University Medical Center Rotterdam, Dept of Surgery[5], Reinier de Graaf Hospital, Delft, The Netherlands*

13.20 Additional value of external ultrasonography of the neck after normal CT-scan in the preoperative assessment of patients with oesophageal cancer (p. 78)
*J.M.T. Omloo[1], M. van Heijl[1], N.J. Smits[2], C.Y. Nio[2], G.W. Sloof[3], J.J.B. van Lanschot[1]. Depts of Surgery[1], Radiology[2] and Nuclear Medicine[3], Academic Medical Centre, University of Amsterdam, The Netherlands*

13.30 The role of Immunoglobulin M, C-reactive protein and complement in liver ischemia-reperfusion injury (p. 79)
*G.M.P. Diepenhorst[1], W. de Graaf[1], H.W. Niessen[2], A.K. van Vliet[1], T.M. van Gulik[1]. Dept of Surgery[1], Surgical Laboratory, Academic Medical Center, Amsterdam, Depts of Cardiology and Pathology[2], University Hospital Vrije Universiteit, Amsterdam, The Netherlands*

13.40 Anaesthesiological considerations on small-incision and laparoscopic cholecy-stectomy in symptomatic cholecystolithiasis: implications on pulmonary function in a randomized clinical trial (p. 80)
*F. Keus[1], J.A. Roukema[2], G.J. Noordergraaf[3], H.G. Gooszen[4], C.J.H.M. van Laarhoven[5]. Dept of Surgery[1], Diakonessenhuis, Dept of Surgery[4], University Medical Center Utrecht, Utrecht, Dept of Surgery[2,5] and Anaesthesiology[3], St Elisabeth hospital, Tilburg, The Netherlands*

13.50 Cost-minimisation analysis in a blind randomised trial on small-incision versus laparo-scopic cholecystectomy from a societal perspective. Sick leave outweighs efforts in hospital savings (p. 81)
*F. Keus[1], T. de Jonge[2], H.G. Gooszen[3], E. Buskens[4], C.J.H.M. van Laarhoven[5]. Dept of Surgery[1], Diakonessenhuis, Utrecht, Dept of Surgery[3], University Medical Center Utrecht, Utrecht, Depts of Surgery[5] and Finance[2], St Elisabeth hospital, Tilburg, Dept of Surgery[4], Julius Center, Utrecht, The Netherlands*

14.00 Timing of cholecystectomy after endoscopic sphincterotomy for common bile duct stones (p. 82)
*A.H.W. Schiphorst[1], M.G.H. Besselink[1,3], D. Boerma[1], R. Timmer[2], M.J. Wiezer[1], K.J. van Erpecum[4], I.A.M.J. Broeders[3], B. van Ramshorst[1]. Dept of Surgery[1] and Gastroenterology[2], St. Antonius Hospital, Nieuwegein, Dept of Surgery[3] and Gastroenterology[4], University Medical Centre Utrecht, The Netherlands*

14.10 Postoperative enteral feeding after pancreatoduodenectomy (p. 83)
*K. Harmsen, M.I. van Berge Henegouwen, O.R.C. Busch, D.J. Gouma, Dept of Surgery, Academic Medical Center, The Netherlands*

14.20 Extracapsular lymph node involvement in node positive patients with adenocarcinoma of the ampulla of Vater (p. 84)
*N.A. van der Gaag[1], S.M. Lagarde[1], O.R.C. Busch[1], T.M. van Gulik[1], F.J.W. ten Kate[2], D.J. Gouma[1], Depts of Surgery[1] and Pathology[2], Academic Medical Centre, Amsterdam, The Netherlands*

14.30 Indication, utilization, and yield of early CT scan in the management of acute pancreatitis (p. 85)
*B.W.M. Spanier[1], M.G.W. Dijkgraaf[2], M.J. Bruno[1]. Depts of Gastro-enterology and Hepatology[1], and Clinical Epidemiology, Biostatistics and Bioinformatics[2], Academic Medical Center, Amsterdam, The Netherlands*

*Donderdag 22 maart 2007*

14.40 Premature closure of the Dutch Stent-in I trial: Colonic stenting vs. surgery in left-sided colonic obstruction for incurable colorectal cancer (p. 86)
*J.E. van Hooft[1], P. Fockens[1], A.W. Marinelli[2], R. Timmer[3], A.M. van Berkel[4], W.A. Bemelman5. Depts of Gastroenterology[1] and Surgery[5], Academic Medical Center, Amsterdam, Dept of Surgery[2], Medical Center Haaglanden, Den Haag, Dept of Gastroenterology[3], St Antonius Hospital, Nieuwegein, Dept of Gastroenterology[4], Rode Kruis Hospital, Beverwijk, The Netherlands*

14.50 The prognostic significance of extracapsular lymph node involvement in node positive patients with colonic cancer (p. 87)
*J. Wind[1], J. Kiewit[1], F.J.W. ten Kate[2], S.M. Lagarde[1], J.J.B. van Lanschot[1], W.A. Bemelman[1]. Depts of Surgery[1] and Pathology[2], Academic Medical Center, Amsterdam, The Netherlands*

15.00 Einde programma, theepauze

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**Nederlandse Vereniging voor Hepatologie** **Parkzaal**

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**Voorzitter:** P.L.M. Jansen

15.00 ***Algemene ledenvergadering***
Nederlandse Vereniging voor Hepatologie

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**Nederlandse Vereniging voor Hepatologie** **Parkzaal**

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Clinical Symposium
**"New Developments in Hepatobiliary Disease"**

**Chairs:** K.J. van Erpecum en E.A.J. Rauws

15.30 Introduction
*Dr. K.J. van Erpecum, Dept of Gastroenterology, University Medical Center Utrecht*

15.32 Endosonography, ERCP and cholangioscopy for bile duct stones
*Dr. M.P. Schwartz, Dept of Gastroenterology, Meander Medical Center, Amersfoort*

15.50 Radiological interventions to remove bile duct stones: more than a last resort?
*Prof. dr. J.S. Laméris, Dept of Radiology, Academical Medical Centre, Amsterdam*

16.10 Bile duct stones: will the surgeon take the lead again?
*Dr. P.M.N.Y.H. Go, Dept of Surgery, St. Antonius Hospital, Nieuwegein*

16.25 Evidence-based medicine and treatment of bile duct stones
*Dr. C.J.H.M. van Laarhoven, Dept of Surgery, St. Elisabeth Hospital, Tilburg*

16.40 New aspects in treatment of primary sclerosing cholangitis
*Prof. dr. U. Beuers, Academic Medical Centre, Amsterdam*

17.00 **State of the Art Lecture**
Cholangioscopy to distinguish between benign and malignant dominant strictures in primary sclerosing cholangitis
*J. Wedemeyer, Dept of Gastroenterology, Hepatology and Endocrinology, Medizinische Hochschule Hannover*

17.30 End of programme

*Donderdag 22 maart 2007*

**Presidential Selection (plenaire sessie)** **Brabantzaal**

**Voorzitter:** J.B.M.J. Jansen

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

20.00 Mucosal delivery of recombinant Hedgehog protein reduces the incidence of intestinal polyp formation (p. 88)
*S.A. Bleuming[1], L.L. Kodach[1], J.C. Hardwick[1,2], S. Rosekrans[1], S.J. van Deventer[1], D.W. Hommes[1,2], M.P. Peppelenbosch[2], P. Rottiers[3], G.R. van den Brink[1,2]. Centre of Experimental and Molecular Medicine[1], Dept of Gastroenterology[2], Academic Medical Centre (AMC) Amsterdam, The Netherlands, Dept for Molecular Biomedical Research, Ghent University and Flanders Interuniversity Institute for Biotechnology[3], (VIB), Belgium*

20.15 Adequately dosed 6-TG use in chronic intestinal inflammation is not associated with nodular regenerative hyperplasia: a series of 73 liver biopsies (p. 89)
*B. Jharap[1], C.J.J. Mulder[1], G. den Hartog [2], B. D. Westerveld[3], L.G.J.B. Engels[4], D.J. de Jong[5], A.A. van Bodegraven[1], N.K.H. de Boer[1], Dept of Gastroenterology and Hepatology[1], VU University Medical Center, Amsterdam, Rijnstate Hospital[2], Arnhem, Isala Clinics[3], Zwolle, Maasland Hospital[4], Sittard, Radboud University[5], Nijmegen, The Netherlands*

20.30 A Prospective Follow-up Study on 163 Patients with Budd-Chiari Syndrome:Results From The European Network for Vascular Disorders of the Liver (EN-Vie) (p. 90 + 91)
*S. Darwish Murad[1], A. Plessier[2], M. Hernandez-Guerra[3], M. Primignani[4], E. Elias[5], M. Bahr[6], A. Hadengue[7], P. Langlet[8], H. Miranda[9], J.C. Garcia-Pagan[3], D.C. Valla[2], H.L.A. Janssen[1]. Dept of Gastroenterology and Hepatology[1], Erasmus University Medical Center Rotterdam, The Netherlands, Hepatology[2], Hopital Beaujon, AP-HP, INSERM-U773 & University Paris-7, Clichy, France, Hepatic Hemodynamic Laboratory[3], Liver Unit, Hospital Clinic, Barcelona, Spain, Gastroenterology and Gostrointestinal Endoscopy Unit[4], Ospedale Poloclinico, Mangiagalli and Regina Elena Foundation, Milan, Italy, Liver Unit[5], Queen Elisabeth Hospital Birmingham, United Kingdom, Depts of Gastroenterology, Hepatology, and Endocrinology[6], Hannover Medical School, Hannover, Germany.*

*Div. of Gastroenterologie and Hepatology[7], Geneva University Hospitals, Geneva, Switzerland, Dept of Hepatogastroenterology[8], Centre Hospatalier Universitaire Brugmann, Bruxelles, Belgium, Liver Transplantation Unit[9], Hospital General Santo Antonio, Porto, Portugal*

20.45 Prophylaxis of post-ERCP pancreatitis: a randomized, placebo controlled trial using intravenous infusion of semapimod, a mitogen activated protein kinases inhibitor (p. 92)

*D.J. van Westerloo[1,2,4], E.A. Rauws[1], D. Hommes[1], A.F. de Vos[2], T. van der Poll[2], M. Dijkgraaf[3], M.J. Bruno[1]. Dept of Gastroenterology[1], Center for Experimental and Molecular Medicine[2] and Dept of Clinical Epidemiology[3], Biostatistics and Bioinformatics, Academic Medical Center, University of Amsterdam, Onze Lieve Vrouwe Gasthuis, Dept of Internal Medicine[4], Amsterdam, The Netherlands*

21.00 ***Ledenvergadering Nederlandse Vereniging voor Gastroenterologie***

*Vrijdag 23 maart 2007*

**Casuïstiek** **Brabantzaal**

**Voorzitter:** W. Hameeteman

08.30 Casuïstische patiëntenbespreking

**Sectie Gastrointestinale Endoscopie** **Brabantzaal**

**Voorzitters:** J.J.G.H.M. Bergman en H.M. van Dullemen

**"Nieuwe technieken in ERCP"**

09.00 Voerdraden in ERCP: nieuwe draden en nieuwe systemen
*Dr. J.W. Poley, maag-darm-leverarts, Erasmus Medisch Centrum, Rotterdam*

09.15 Nieuwe cannulatietechnieken: catheter, guide wire of cannulotoom
*Dr. M.J. Bruno, maag-darm-leverarts, Academisch Medisch Centrum, Amsterdam*

09.30 Einde van dit programma-onderdeel

**Sectie Gastrointestinale Endoscopie** **Brabantzaal**

**Voorzitter:** W. Hameeteman

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

09.30 Nurse endoscopy: preliminary evaluation of a colonoscopy training program (p. 93)
*J.J. Koornstra, H.M. van Dullemen. Dept of Gastroenterology and Hepatology, University Medical Center Groningen, The Netherlands*

09.40 Screening and surveillance for colorectal carcinoma in patients with ulcerative colitis and Crohn's disease: Are current surveillance guidelines adequate? Interim analysis of a retrospective multi-centre descriptive study (p. 94) *M.W.M.D. Lutgens[1], F.P.Vleggaar[1], B. Oldenburg[1], M.E.I. Schipper[2], P.C.F. Stokkers[3], C.J. van der Woude[4], G. Dijkstra[5], D.J. de Jong[6], M. Samsom[1]. Depts of Gastroenterology[1] and Pathology[2], University Medical Center Utrecht, Academic Medical Center Amsterdam[3], Erasmus Medical Center Rotterdam[4], University Medical Center Groningen[5], St. Radboud Medical Center Nijmegen[6], The Netherlands*

09.50 Endoscopic TriModality Imaging (ETMI) for the detection and classification of colonic polyps (p. 95)
*F.J.C. van den Broek, J.C. Hardwick, J.B. Reitsma, M.A. Kara, P. Fockens, E. Dekker. Dept of Gastroenterology and Hepatology, Academic Medical Centre Amsterdam, the Netherlands.*

10.00 Koffiepauze expositiehal

10.30 Endoscopic Tri-Modality Imaging improves the detection of high-grade dysplasia and early cancer in Barrett's esophagus; an international multi-center feasibility study (p. 96)
*W.L. Curvers[1], K. Ragunath[2], L.M. Wong Kee Song[3] , H.C. Wolfsen[4], K. Wang[3], M.B. Wallace[4], P. Fockens[1], J.J.G.H.M. Bergman[1]. Academic Medical Center[1], Amsterdam, The Netherlands, Queens Medical Centre[2], Nottingham University Hospitals NHS Trust, United Kingdom, Mayo Clinic, Rochester[3], Mayo Clinic[4], Jacksonville, United States*

10.40 Radiofrequency Ablation of Barrett's Esophagus Containing High-Grade Dysplasia (p. 97)
*J.J.Gondrie[1], F.P. Peters[1], W.L. Curvers[1], R.E. Pouw[1], C.M. Sondermeijer[1], F. ten Kate[2], K.K. Krishnadath[1], P. Fockens[1], J.J. Bergman[1]. Depts of Gastroenterology[1] and Pathology[2], Academic Medical Center, Amsterdam, The Netherlands*

10.50 Stepwise radical endoscopic resection for complete removal of Barrett's esophagus with early neoplasia: a prospective study of 56 patients with 2 years follow-up (p. 98)
*R.E. Pouw[1], F.P. Peters[1], W.L. Curvers[1], W.D. Rosmolen[1], F.J.W. ten Kate[2], K..K. Krishnadath[1], P. Fockens[1], J.J.G.H.M. Bergman. Depts of Gastroenterology and Hepatology[1], and Pathology[2], Academic Medical Center, Amsterdam, The Netherlands*

*Vrijdag 23 maart 2007*

11.00 New design stents for the palliation of dysphagia in patients with irresectable esophageal or gastric cardia carcinoma: a randomized study (p. 99) *E.M.L. Verschuur[1], A. Repici[2], E.W. Steyerberg[3], E.J. Kuipers[1], P.D. Siersema[1]. Depts of Gastroenterology & Hepatology[1] and Public Health[2]. Erasmus MC University Medical Center Rotterdam, The Netherlands, Dept of Gastroenterology & Hepatology[2], Instituto Clinico Humanitas Milan, Italy*

11.10 Efficacy of a new nitinol enteral stent (WallFlex) in malignant gastric outlet obstructtion: a prospective, open, multicenter clinical trial (p. 100)
*J.E. van Hooft[1], M.J. Uitdehaag[2], M.J. Bruno[1], M. Dijkgraaf[3], R. Timmer[4], P.D. Siersema[2], P. Fockens[1]. Depts of Gastroenterology[1] and Clinical Epidemiology and Bio-statistics[3], Academic Medical Center, Amsterdam, Dept of Gastroenterology[2], Erasmus MC University Medical Center Rotterdam[4], Dept of Gastroenterology, St. Antonius Hospital, Nieuwegein, The Netherlands*

11.20 EUS-Guided trucut biopsy versus EUS-guided fine needle aspiration; an evaluation of 67 patients with mediastinal lesions (p. 101).
*R.C.H. Scheffer[1], M.F.J. Stolk[1], C.A. Seldenrijk[2], P. de Bruin[2], R. Timmer[1], B.L.A.M. Weusten[1]. Depts of Gastroenterology[1] and Pathology[2], St. Antonius Hospital, Nieuwegein, The Netherlands*

11.30 Endoscopic treatment of bile duct injury: long term outcome and predictors for success. (p. 102)
*P.R. de Reuver[1], E.A.J. Rauws[2], M. Vermeulen[1], D.J. Gouma[1], M.J. Bruno[2]. Depts of Surgery[1] and Gastroenterology[2], Academic Medical Centre, Amsterdam, The Netherlands*

11.40 Endoscopic ultrasonography: a valuable tool in screening high-risk patients for pancreatic cancer (p. 103)
*J.W. Poley[1], A. Wagner[2], C.H.J. van Eijck[3], E.J. Kuipers[4]. Depts of Gastroenterology and Hepatology[1], Clinical Genetics[2], Surgery[3], and Gastroenterology and Hepatology[4], Erasmus MC, University Medical Center, Rotterdam, The Netherlands*

11.50 Endoscopic ultrasound guided transmural debridement of symptomatic organized pancreatic necrosis (p. 104)
*R.P. Voermans[1], M.C. Veldkamp[1], E.A.J. Rauws[1], M.J. Bruno[1], P. Fockens[1]. Dept Gastroenterology and Hepatology[1], Academic Medical Center, Amsterdam, The Netherlands*

12.00 Lunchbuffet in de expositiehallen

**Nederlandse Vereniging voor Gastroenterologie** **Baroniezaal**

**Voorzitters:** E.C. Klinkenberg en P.D. Siersema

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

08.30 Why do subjects decline colorectal cancer screening by FOBT? (p. 105)
*A.F. van Rijn[1], M. Deutekom[2], P. Fockens[1], P. Bossuyt[2], L. van Rossum[3], R. Laheij[3], J. Jansen[3], E. Dekker. Depts of Gastroenterology[1] and Clinical Epidemiology and Biostatistics[2], Academic Medical Center, University of Amsterdam, Dept of Gastroenterology[3], Radboud University of Nijmegen, The Netherlands*

08.40 The incidence of hereditary non-polyposis colorectal carcinoma related cancer in clinically ascertained MLH1, MSH2 and MSH6 families (p. 106)
*D. Ramsoekh[1], M.E. van Leerdam[1], A. Wagner[2], D. Dooijes[2], C. Tops[3], E.J. Kuipers[1]. Depts of Gastroenterology and Hepatology[1] and Clinical Genetics[2], Erasmus MC University Medical Center, Rotterdam, Dept of Human and Clinical Genetics[3], Leiden University Medical Center, Leiden, The Netherlands*

08.50 The use of genetic testing in (attenuated) familial adenomatous polyposis families (p. 107)
*D. Ramsoekh[1], A. Wagner[2], M.E. van Leerdam[1], D. Dooijes[2], C. Tops[3], E.J. Kuipers[1]. Depts of Gastroenterology and Hepatology[1] and Clinical Genetics[2], Erasmus MC University Medical Center, Rotterdam, Dept of Human and Clinical Genetics[3], Leiden University Medical Center, Leiden, The Netherlands*

09.00 Induction of caspase-8 and cFLIP expression during colorectal carcinogenesis in sporadic and HNPCC adenomas and carcinomas (p. 108)
*D.M. Heijink[1], J.H. Kleibeuker[2], M. Jalving[1,2], W. Boersma-van Ek[2], J.J. Koornstra[2], J. Wesseling[3], S. de Jong[1]. Dept of Medical Oncology[1], and Gastroenterology and Hepatology[2], University Medical Center Groningen, University of Groningen, Dept of Pathology[3], Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands*

*Vrijdag 23 maart 2007*

09.10 Redesigning the process of colorectal cancer care: impact on quality of care and cost. (p. 109)
*F. Vaessen[2], D. Walta[1,5], M. Nap[3], P. Platteel[1], H. van der Bijl[5], J. Wals[4], M. Sosef[5], J.G. Goedhard[1], P.J. van der Schaar[1]. Depts of Gastroenterology[1], Health Care Innovation[2], Pathology[3], Oncology[4] and Surgery[5], Atrium Medical Center, Heerlen, The Netherlands*

09.20 DNA copy number profiles of primary colorectal cancers as predictors of response to therapy (p. 110)
*C. Postma[1], M. Koopman[2], B. Carvalho[1], T.E. Buffart[1], P.P. Eijk[1], G.J. Peters[3], B. Ylstra[1], J.H.J.M. van Krieken[4], C.J.A. Punt[2], G.A. Meijer[1]. Depts of Pathology[1] and Oncology[3], VU Medical Center, Amsterdam, Depts of Medical Oncology[2] and Pathology[4], University Medical Center St. Radboud, Nijmegen, The Netherlands*

09.30 Performance characteristics of faecal occult blood tests: which test to use for colorectal cancer screening? (p. 111)
*J.S. Terhaar Sive Droste[1], M.E. Craanen[1], R.W.M. van der Hulst[2], L. de Baaij[1], A.C.T.M. Depla[3], R.J.L.F. Loffeld[4], E.M. Mutsaers[1], S. van der Reijt[1], P. Snel[3], R.L.J. van Wanrooy[1], C.J.J. Mulder[1]. Dept of Gastroenterology and Hepatology, VU Medical Center, Amsterdam, Kennemer Gasthuis[2], Haarlem, Slotervaart Ziekenhuis[3], Zaans Medical Center[4], Zaandam, The Netherlands*

09.40 Development of an RNA-based fecal screening panel test for colorectal cancer (p. 112)
*A.F. van Rijn[1], C. Lauppe[1], E. Dekker[1], M. Beld[2], R. Minnaar[2], J. Hardwick[1]. Dept of Gastroenterology & Hepatology[1], Laboratory of Clinical Virology[2], Dept of Medical Microbiology, Academic Medical Center, University of Amsterdam, The Netherlands*

09.50 Analytic sensitivity of faecal DNA testing for colorectal cancer (p. 113)
*L.J.W. Bosch[1], J. Terhaar Sive Droste[2], S. Mongera[1], C.J. Mulder[2], M.E. Craanen[2], B. Carvalho[1], G.A. Meijer[1]. Depts of Pathology[1] and Gastroenterology[2], VU Medical Center, Amsterdam, The Netherlands*

10.00 Koffiepauze

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

10.30 Acid suppression normalizes the expression of mucosal repair associated genes in the esophageal epithelium of GERD patients (p. 114)
*D.R. de Vries[1], J.J.M. ter Linde[1], M.A. van Herwaarden[1], P. Shephard[2], M.M. Geng[2], H.P. Hoffman[2], T. Klein[2], S. Postius[2], M.P. Schwartz[1], M. Samsom[1]. University Medical Center Utrecht[1], Utrecht, The Netherlands, Altana Pharma AG[2], Konstanz, Germany*

10.40 Adherence to gastroprotection and the risk of NSAID-related upper gastrointestinal complications (p. 115)
*E.M. van Soest[1,2], M.J.C.M. Sturkenboom[2,3], J.D. Dieleman[2], K.C. Verhamme[2], P.D. Siersema[1], E.J. Kuipers[1]. Dept of Gastroenterology and Hepatology[1], Medical Informatics[2], and Epidemiology and Biostatistics[3], Erasmus University Medical Center, Rotterdam, The Netherlands*

10.50 Step-down is equally effective as step-up as initial management of new onset dyspepsia in Dutch primary care (p. 116)
*C.J. van Marrewijk[1], R.J.F. Laheij[1], S. Mujakovic[2], G.A.J. Fransen[3], J.W. Muris[3], N.J. de Wit[2], M.E. Numans[2], A.J. Knottnerus[3], J.B.M.J. Jansen[1]. Dept of Gastroenterology and Hepatology[1], Radboud University Nijmegen Medical Center, Nijmegen, Julius Center for Primary Care and Health Sciences[2], Utrecht UMC, Utrecht, Research Institute Caphri, Dept of General Practice[3], Maastricht University, Maastricht, The Netherlands*

11.00 Proton pump inhibitor use increases the risk of severe community-acquired infections. (p. 117)
*R.J.F. Laheij[1], L.E. Targownik[2], S. Leung[2], C. Metge[3], M.G.H. van Oijen[1], J.P.H. Drenth[1], J.B.M.J. Jansen[1]. Dept of Gastroenterology[1], University Medical Center St. Radboud, Nijmegen, The Netherlands, Section of Gastroenterology, Dept of Internal Medicine[2], Manitoba Centre for Health Policy, Dept of Community Health Sciences[3], University of Manitoba, Winnipeg, Manitoba, Canada*

11.10 Neoadjuvant Chemoimmunotherapy with Cisplatin, Gemcitabine plus GM-CSF in Locally Advanced Esophageal Cancer; a Phase II Study (p. 118)
*A.A.F.A. Veenhof, J.J.G. Scheepers, C.J. van Groeningen, G.J. Peters, E. Bloemena, M.E. Craanen, W.J.H.J. Meijerink, M.A. Cuesta. VU University Medical Center, Amsterdam, The Netherlands*

*Vrijdag 23 maart 2007*

11.20 Survival in patients with Refractory Coeliac Disease and Enteropathy associated T cell Lymphoma (p. 119)
*A. Al-toma[1], W.H.M.Verbeek[1], M. Hadithi[1], B.M.E. von Blomberg[2], C.J.J. Mulder[1]. Depts of Gastroenterology[1] and Clinical Pathology[2], VU University Medical Center, Amsterdam, The Netherlands*

11.30 The MYO9B gene is a strong risk factor for the development of refractory coeliac disease* (p. 120)
*V.M. Wolters[1], W.H.M. Verbeek[2], A. Zhernakova[3], C. Onland-Moret[3], M.W.J. Schreurs[4], A.J. Monsuur[3], W. Verduijn[5], C. Wijmenga[3], C.J.J. Mulder[2]. Depts of Pediatric Gastroenterology[1], UMC Utrecht, Gastro-enterology[2], VUmc Amsterdam, Complex Genetics Section[3], DBG-Dept of Medical Genetics, UMC Utrecht, Utrecht, Pathology[4], VUmc Amsterdam, Immuno-haematology and Bloodtransfusion[5], LUMC, Leiden, The Netherlands*

11.40 Marsh II enteropathy: identifying gluten sensitivity by gluten free diet and gluten challenge (p. 121)
*R.S. de Vries[1], M.S. Goerres[1], K.F. Kok[1], J.W.R. Meijer[2], R.A. de Vries[1], C.J.J. Mulder[3], P.J. Wahab[1]. Depts Gastroenterology & Hepatology[1] and Pathology[2], Rijnstate Hospital Arnhem, Dept of Gastroenterology & Hepatology[3], Free University Hospital Amsterdam, The Netherlands*

11.50 Flowcytometry of intestinal T cells in Refractory Coeliac Disease (p. 122)
*WHM Verbeek[1], MS Goerres[3], MWJ Schreurs[2], PET Scholten[2], BME von Blomberg[2], CJJ Mulder[1]. Depts of Gastroenterology[1] and Pathology[2], VU University Medical Center, Amsterdam, Dept of Gastroenterology[3], Rijnstate Hospital, Arnhem, The Netherlands*

12.00 Lunchbuffet in expositiehallen

**Sectie Experimentele Gastroenterologie** **Auditorium**

**Voorzitter:** J.G. Kusters en G. Dijkstra

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

08.30 Association of Runt-Related Transcription Factor 3 (RUNX3) and Organic Cation Transporters 1 and 2 (OCTN1/2) with Inflammatory Bowel Disease (p. 123)

*R.K. Weersma[1], L. Zhou[1], I. M. Nolte[2], G. van der Steege[2], H.M. van Dullemen[1], E. Oosterom[2], L. Bok[1], K.N. Faber[1], M.P. Peppelenbosch[3], J.H. Kleibeuker[1], G. Dijkstra[1]. Depts of Gastroenterology and Hepatology[1], Pathology and Laboratory Medicine[2], Section Medical Biology, and Cell Biology[3], section Immunology, University Medical Center Groningen, The Netherlands*

08.40 A large, nationwide, case-control study for the association of DLG5, OCTN1/2 and CARD15 with Inflammatory Bowel Diseases in the Netherlands. (p. 124 + 125)

*R.K. Weersma[1], P.C.F. Stokkers[2], .A.A van Bodegraven[3], R.A. van Hogezand[4], H.W. Verspaget [4], D.J.de Jong[5], C. J. van der Woude[6], B. Oldenburg[7], R.K. Linskens[8], G. van der Steege[9], D.W. Hommes[4], C. Wijmenga[10], J.B. Crusius[11], I.M. Nolte[9], G. Dijkstra[1]. On behalf of the Dutch Initiative on Crohn and Colitis (ICC): Dept of Gastroenterology and Hepatology[1], University Medical Center Groningen and University of Groningen, Groningen, Dept of Gastroenterology and Hepatology[2], Academic Medical Center, Amsterdam, Dept of Gastroenterology and Hepatology[3], VU University Medical Center, Amsterdam, Dept of Gastroenterology and Hepatology[4], Leiden University Medical Center, Leiden, Dept of Gastroenterology and Hepatology[5], Radboud University Nijmegen Medical Center, Nijmegen, Dept of Gastroenterology and Hepatology[6], Erasmus Medical Center, Rotterdam, Dept of Gastroenterology and Hepatology[7], University Medical Center, Utrecht, Dept of Gastroenterology and Hepatology[8], St Anna Zorggroep Hospital, Geldrop, Dept of Medical Biology[9], University Medical Center Groningen and University of Groningen, Dept of Medical Genetics[10], University Medical Center, Utrecht, Laboratory for Immunogenetics, Dept of Pathology[11], VU University Medical Center, Amsterdam, The Netherlands*

*Vrijdag 23 maart 2007*

08.50 Bile acid stimulated expression of the Farnsesoid X Receptor enhances the immune response in Barrett Esophagus (p. 126)
*A. Capello, P.D. Siersema, L.M.G. Moons, E.J. Kuipers, J.G. Kusters. Dept of Gastroenterology and Hepatology, Erasmus MC University of Rotterdam, The Netherlands*

09.00 Einde vrije voordrachten

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**Lustrumsymposium Sectie Experimentele Gastroenterologie** **Auditorium**

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**Chairs:** J.G. Kusters en G. Dijkstra

ZonMw ondersteunt ZonMw

**'Celebrate 10 years of Basic Research on Gastrointestinal Disease, future perspectives'**

*English will be the official language for this conference*

09.05 Introduction to the symposium

09.15 'Recent advances in Pediatric Gastroenterology: Scientific and clinical progress in perspective'
*Dr. J.A.J.M. Taminiau, Emma Kinderziekenhuis, Academisch Medisch Centrum, Amsterdam*

09.30 New molecular/immunological insights in the etiology of enteropathies
*Dr. F.M. Ruemmele, Pediatric Gastroenterology, Hepatology and Nutrition, Hôpital Necker - Enfants Malades, Paris, France*

10.00 Koffiepauze

10.30 Did the Characterization of Hepatic Transport Systems help us in understanding Liver Disease?
*Prof. dr. P.L.M. Jansen, Academisch Medisch Centrum, Amsterdam*

10.45 Enterohepatic receptors in health and disease
*Dr. K. Schoonjans, Institut de Genetique et de Biologie Moleculaire et Cellulaire, Illkirch, France*

11.15 Is there life after antibodies?
*Prof. dr. S.J.H. van Deventer, Academisch Medisch Centrum, Amsterdam*

11.30 Live genetic modified organisms: designer therapeutics for the future
*Prof. dr. L. Steidler, Director Technology Development, ActoGeniX NV, Belgium*

12.00 End of Symposium

12.00 ***Ledenvergadering Sectie Experimentele Gastroenterologie***

12.30 Lunchbuffet in expositiehal

## Presentaties MLDS-projecten — Brabantzaal

**Voorzitters:** E.H.H.M. Rings en E. Nieuwenhuis

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

13.30 Behavioral therapy for treatment of childhood constipation: A randomized controlled trial. MLDS project no. SWO 02-16 (p. 127)
*M. van Dijk[1], M.E.J. Bongers[2], G.J. de Vries[3], M.A. Grootenhuis[1], B.F. Last[1,4], M.A. Benninga[2]. Psychosocial Dept[1], Dept of Pediatric Gastroenterology and Nutrition[2], Emma Children's Hospital/Academic Medical Center, University of Amsterdam, Dept of Psychiatry[3], Academic Medical Centre, University of Amsterdam, Dept of Developmental Psychology[4], Vrije Universiteit Amsterdam, The Netherlands*

13.45 MYH-based strategy towards identification of novel genes somatically mutated during intestinal tumor progression, MLDS project no. MWO 04-21 (p. 128)
*P. Alberici, M. Bevelander, C. Gaspar, M. van der Valk, R. Fodde. Josephine Nefkens Instituut, Erasmus University Medical Center Rotterdam, The Netherlands*

## Sectie Experimentele Gastroenterologie — Brabantzaal

**Voorzitters:** E.H.H.M. Rings en E. Nieuwenhuis

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

14.00 The Sab adhesins of Helicobacter pylori: acid-responsive regulation of expression and their role in the modulation of the host immune response (p. 129)
*A.M. Rolloos[1], R. de Jonge[1], R.M. Peek Jr.[2], D.A. Israel[2], C. Kelton[2], J.G. Kusters[1], E.J. Kuipers[1], A.H.M. van Vliet[1]. Erasmus MC-University Medical Center[1], Rotterdam, The Netherlands, Vanderbilt University School of Medicine[2], Nashville, Tennessee, USA*

14.10 Oral administration of alkaline phosphatase ameliorates colitis (p. 130)
*A. Tuin[1], A. de Jager-Krikken[1], L. Bok[2], W. Raaben[3], M.P. Velders[3], D.K.F. Meijer[1], K. Poelstra[1], G. Dijkstra[2]. Dept of Pharmacokinetics and Drug Delivery[1], University Centre for Pharmacy, University of Groningen, Dept of Gastroenterology and Hepatology[2], University Medical Centre Groningen, AM-Pharma, Bunnik[3], The Netherlands*

14.20 The specific nicotinic $\alpha$7 receptor agonist AR-R17779 reduces inflammation in a mouse model of DSS colitis (p. 131)
*S.A. Snoek[1], M.I. Verstege[1], E.P. van der Zanden[1], G. la Rosa[2], G.E. Boeckxstaens[1], A.A. te Velde[1], W.J. de Jonge[1,3]. Dept of Gastroenterology and Hepatology[1], Academic Medical Center, Amsterdam, The Netherlands, Critical Therapeutics[2], Inc., Lexington, MA, USA., Sir William Dunn School of Pathology[3], University of Oxford, United Kingdom*

14.30 Differential transcriptional responses of intestinal mucosa upon intake of log-phase, stationary and dead cells of Lactobacillus plantarum WCFS1 in vivo in humans (p. 132)
*F.J. Troost[1,2], P. van Baarlen[2,3], M. Kleerebezem[2,4], P. Lindsey[5], W.M. de Vos[2,6], R-J.M. Brummer[2,7]. Dept of Internal Medicine, div. of Gastroenterology & Hepatology[1], Nutrition and Toxicology Research Institute Maastricht (NUTRIM), Maastricht University, Maastricht, Wageningen Center for Food Sciences[2], Wageningen, Center for Molecular and Biomolecular Informatics[3], Radboud University Nijmegen, Nizo Food Research[4], Ede, Genome Centre Maastricht, Dept of Population Genetics[5], Nutrition and Toxicology Research Intstitute Maastricht, Maastricht University, Maastricht, Dept of Microbiology[6], Wageningen University and Research, Wageningen, Depts of Internal Medicine and Clinical Dietetics[7], NUTRIM, University Hospital Maastricht, The Netherlands*

14.40 Gastric Helicobacter species colonizing strict carnivores express two different, functional urease enzymes (p. 133)
*J. Stoof, S. Breijer, R.G.J. Pot, E.J. Kuipers, J.G. Kusters, A.H.M. van Vliet. Dept of Gastroenterology and Hepatology, Erasmus MC-University Medical Center, Rotterdam, The Netherlands*

14.50 *Gpx2* and *Aqp8* as new markers for colonic inflammation in experimental colitis and IBD: an important role for $H_2O_2$? (p. 134)
*A.A. te Velde[1], I. Pronk[1], F. de Kort[1], P.C.F. Stokkers[2]. Laboratory of Experimental Internal Medicine[1], Dept of Gastroenterology[2], Academic Medical Center, Amsterdam, The Netherlands*

15.00 Einde programma

**Nederlandse Vereniging voor Hepatologie (klinisch) Baroniezaal**

**Voorzitters:** J.P.H. Drenth en R.J. de Knegt

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

13.30 Withdrawal flares after treatment with peginterferon alpha-2b alone or in combination with lamivudine in HBeAg-positive chronic hepatitis B (p. 135)
*E.H.C.J. Buster[1], H.J. Flink[1], B.E. Hansen[1,2], S.W. Schalm[1], H.L.A. Janssen[1]. Depts of Gastroenterology and Hepatology[1], and Epidemiology and Biostatistics[1], Erasmus MC University Medical Center Rotterdam, The Netherlands*

13.40 High prevalence of hepatitis C in the general Dutch population (p. 136)
*S. Slavenburg[1], F. Verduyn-Lunel[2], J.P.H. Drenth[3]. Dept of Gastroenterology & Hepatology Radboud University Nijmegen Medical Center, The Netherlands*

13.50 Limited role for routine ascitic culture as a diagnostic tool for spontaneous bacterial peritonitis in the era of prophylactic antibiotics (p. 137)
*J.J. Kuiper, H.R. van Buuren, R.A. de Man. Dept of Gastroenterology and Hepatology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands*

14.00 In Primary Sclerosing Cholangitis the long-term risk for colorectal cancer is more than twofold higher than the risk for cholangiocarcinoma. Results of a long-term cohort study (p. 138)
*M.M.H. Claessen[1], F.P. Vleggaar[1], K.M.A.J. Tytgat [1], M. Samsom[1], H.R. van Buuren[2]. Depts of Gastroenterology, University Medical Center Utrecht[1] and Erasmus Medical Center, Rotterdam[2], The Netherlands*

14.10 Cysts of *PRKCSH* mutated polycystic liver disease patients lack hepatocystin but over-express MUC1 (p. 139)
*E. Waanders[1], C.N. Maass[2], J.H.J.M. Van Krieken[2], J.P.H. Drenth[1]. Depts of Gastroenterology and Hepatology[1], and Pathology[2], Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands*

14.20 Biliary drainage attenuates post-ischemic reperfusion injury in the cholestatic rat liver (p. 140)
*J.J. Kloek, H.A. Marsman, A.K. van Vliet, D.J. Gouma, T.M. van Gulik. Dept of Surgery, Surgical laboratory, Academic Medical Center, Amsterdam, The Netherlands*

14.30 Non-anastomotic biliary strictures after liver transplantation: novel insights in presentation and pathogenesis (p. 141)
*C.I. Buis[1], R.C. Verdonk[2], E.J. van der Jagt[3], C.S. van der Hilst[4], M.J.H. Slooff[1], E.B. Haagsma[2], R.J. Porte[1]. Hepatobiliary Surgery and Liver Transplantation[1], Depts of Hepatology[2] and Radiology[3], University Medical Center Groningen, Groningen, The Netherlands*

14.40 $^{99m}$TC-GSA scintigraphy with SPECT in the assessment of hepatic function and functional volume during liver regeneration in a rat model (p. 142)
*W. de Graaf[1], R.L. Vetelainen[1], A.K. van Vliet[1], R.J. Bennink[2], T.M. van Gulik[1]. Dept of Surgery/Surgical Laboratory[1] and Nuclear Medicine[2], Academic Medical Center, University of Amsterdam, The Netherlands*

14.50 Osteoclast-like Cell Formation from Peripheral Blood Mononuclear Cells of Chronic Liver Disease Patients with Osteopenia. (p. 143)
*B.J. Olivier[1,2,3], T. Schoenmaker[4,5], R.E. Mebius[3], V. Everts[5], C.J. Mulder[6], K.M.J. van Nieuwkerk[6], T.J. de Vries[4,5], S.W. van der Merwe[1]. Hepatology Research[1] & Dept of Chemical Pathology[2], University of Pretoria, Pretoria, South Africa, MCBI[3], VUmc, Depts of Periodontology[4] and Oral Cell Biology[5] & ACTA, UvA & VU, Amsterdam, Dept of Gastroenterology & Hepatology[6], VUmc, Amsterdam, The Netherlands*

15.00 Theepauze

**Sectie Experimentele Gastroenterologie** **Auditorium**

**Voorzitters:** E.A.F. van Tol en G. Bouma

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

13.30 Barrett's epithelium is associated with a specific bacterial flora in the esophagus (p. 144)
*V. Menke, E.J. Kuipers, L.M.G. Moons, B. van den Bogert, K.P.M. van Zoest, P.D. Siersema, J.G. Kusters. Dept of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands*

13.40 The xenobiotic sensor PXR is associated with Barrett's esophagus (p.145)
*A. van de Winkel[1], L.M.G. Moons[1], V. Menke[1], A. Capello[1], R.G.J. Pot[1], H. van Dekken[2], E.J. Kuipers[1], P.D. Siersema[1], J.G. Kusters[1]. Depts of Gastroenterology and Hepatology[1], and Pathology[2], Erasmus MC - University Medical Center, Rotterdam, The Netherlands*

13.50 Germline hypermethylation of the MLH1 promotor region as the cause of Lynch syndrome (p. 146)
*R.C. Niessen[1], R.M.W. Hofstra[1], K. Kooi[1], J. Ou[1], A. Ferreira[1], M.J.W. Berends[1], H. Hollema[2], J.H. Kleibeuker[3], R.H. Sijmons[1]. Dept of Genetics[1], Pathology[2] and Gastroenterology[3], University Medical Center Groningen, University of Groningen, The Netherlands*

14.00 Effect of the immune response during the early phases of Barrett's Esophagus development (p. 147)
*A. Capello, V. Menke, R.C.M. Kiekens, P.M.H. van Strien, E.J. Kuipers, J.G. Kusters, P.D. Siersema. Dept of Gastroenterology and Hepatology, Erasmus MC - University of Rotterdam, The Netherlands*

14.10 Predisposition to the Th1 immune response is associated with an increased risk for development of Barrett's esophagus (p. 148)
*V. Menke[1], A. Capello[1], J.G. Kusters[1], P.M.H. van Strien[1], L.M.G. Moons[1], R.R. Sital[1], R.W.F. de Bruin[2], E.J. Kuipers[1], P.D. Siersema[1]. Depts of Gastroenterology and Hepatology[1], and Surgery[2], Erasmus MC- University Medical Center, Rotterdam, The Netherlands*

14.20 Regulation of the murine Muc2 mucin gene by HNF-3 factors* (p. 149)
*M. van der Sluis[1*], A. Vincent[2*], J. Bouma[1], A. Korteland-Van Male[1,3], J.B. van Goudoever[1], I.B. Renes[1], I. Van Seuningen[2]. *Both authors participated equally in this study. Depts of Pediatrics[1], Div. of Neonatology, and Pediatrics[3], Div. of Gastroenterology, Erasmus Medical Center-Sophia, Rotterdam, The Netherlands, Unité INSERM No560[2], Lille, France*

14.30 Her-2/neu amplification in esophageal adenocarcinoma as a potent target for cancer immunotherapy (p. 150)
*F. Milano[1], A.M. Rygiel[1], J.J.G.H.M. Bergman[2], P. Fockens[2], W. Rosmolen[2], M. Kapsenberg[3], A. ten Brinke[4], M. van Ham[4], K.K. Krishnadath[2]. Depts of Experimental Internal Medicine[1], Gastroenterology and Hepatology[2], and Cell Biology[3], Academic Medical Center, Amsterdam, Sanquin[4], Amsterdam, The Netherlands*

14.40 Identification of biological pathways involved in colon adenoma to carcinoma progression (p. 151)
*A.H. Hardebol[1], R.J.A. Fijneman[1,2], C. Postma[1], S. Mongera[1], B. Ylstra[1], G.A. Meijer[1], B. Carvalho[1]. Dept of Pathology[1] and Medical Oncology[2], VU Medical Center, Amsterdam, The Netherlands*

14.50 De novo FoxP3 expression in mucosal regulatory T cells that are generated through mucosal antigen application* (p. 152)
*M.F. du Pré[1], L.A. van Berkel[1], W.W.J. Unger, F. Hauet-Broere, E.E.S. Nieuwenhuis[1], G. Kraal, J.N. Samsom[1]. Dept of Paediatrics[1], division Gastroenterology and nutrition Erasmus MC – Sophia Children's Hospital, Rotterdam, The Netherlands*

15.00 Einde programma

*Vrijdag 23 maart 2007*

**Sectie Endoscopie Verpleegkundigen en Assistenten** **Diezezaal**

10.00 Ontvangst

10.30 Hanneke Hagenaars, Erasmus MC, Rotterdam
Donatie van organen binnen Nederland en de rol van Eurotransplant

11.00 Free Papersessie
*SEVA-leden geven een presentatie van 10 minuten, deze zullen door de jury beoordeeld worden en de beste free paper verdient een reisbeurs voor het UEGW in Parijs*

Carlien de Jong, LUMC, Leiden
Meting naar het niet doorgaan van onderzoeken op de scopieafdeling van het LUMC

Agaath Hanrath AMC, Amsterdam
Electronisch zorgdossier

Marlou Stap, Vumc, Amsterdam
Het verpleegkundig PEG spreekuur

Willeke Wandel, St. Jansdalziekenhuis, Harderwijk
Spiegelreflexgesprek bij mensen met coloncarcinoom

Eva Grift, Meander Medisch Centrum, Amersfoort
Rectaal bloedverlies ' Project sneller beter'

12.00 Lunchbuffet in Kempenhal

13.30 Ledenvergadering

14.00 M.J. Bruno, maag-darm-leverarts, AMC, Amsterdam
ERCP voerdraad geleide canulatie

14.30 A. Flierman, maag-darm-leverarts i.o., Isala Klinieken Zwolle
Een grote pens

14.50 A.C. Poen, maag-darm-leverarts,Isala Klinieken Zwolle
Klinische toepassingen van endo-echografie

15.10 Einde programma

**Vereniging voor Maag Darm Lever Verpleegkundigen** **Parkzaal**

**Symposium 'Leverlijden'**

09.30 Ontvangst koffie en thee

10.00 Welkomstwoord en inleiding
*De heer W. Goverde, voorzitter VMDLV*

10.15 Anatomie/fysiologie Scleroserende cholangitis Hepatitis C
*Prof. dr. J.P.H. Drenth, maag-darm-leverarts, UMC St. Radboud Nijmegen*

*De heer R. Perquin, Ervaringsdeskundige*

11.30 Eurotransplant
*Mevr. H. Hagenaars, Transplantatiecoördinator en regionaal teamleider donorwerving, Erasmus MC, Rotterdam*

12.00 Lunch expositiehallen

13.00 Levertransplantatie
*Dr. G. Kazemier, chirurg, Erasmus MC, Rotterdam*

13.30 Verpleegkundige aspecten bij levertransplantatie
*Mevr. A. Wilschut, transplantatieverpleegkundige, Erasmus MC, Rotterdam*

14.00 Voeding bij leverlijden
*Mevr. A. Donker, diëtist, Leids Universitair Medisch Centrum, Leiden*

14.30 Afsluiting
*De heer W. Goverde*

**The influence of active smoking, passive smoking and smoking cessation on the disease course and behaviour of inflammatory bowel disease**

F. van der Heide[1], A. Dijkstra[2], R.K. Weersma[1], F. Albersnagel[3], W.J. Sluiter[4], J.H.Kleibeuker[1] and G. Dijkstra[1]. Depts of Gastroenterology[1], Social and Organizational Psychology[2], Health Psychology[3], and Endocrinology[4]. University Medical Center Groningen, The Netherlands

Smoking has been a known risk factor for inflammatory bowel disease (IBD), but with a remarkable opposite effect on Crohn's disease (CD) and ulcerative colitis (UC). Smoking aggravates CD and improves UC. In this study we extensively studied the influence of smoking on both the disease course and behaviour. Medical charts of 864 patients were retrospectively reviewed concerning smoking behaviour, disease course, extraintestinal manifestations, disease location and behaviour and all patients received an additional questionnaire concerning smoking behaviour, passive smoking, education, influence of disease on smoking behaviour and smoking cessation plans. At the end of follow up (median 9 years) of the 864 patients (490 CD, 354 UC, 20 IC), 24 (3%) were deceased and 693 (83%) responded to the questionnaire. In UC 30% and in CD 13% had stopped smoking before diagnosis. The diagnosis did not change smoking behaviour in 45% CD and 22% UC patients, but smoking cessation (13% vs 9%) and stop plans (89% vs 89%) were not different between CD and UC patients. There was no difference in outcome for smoking in CD patients. Smoking UC patients had a lower colectomy rate (12% vs 28%;$p<0.02$), less primary sclerosing cholangitis (PSC) (3% vs 13%;$p=0.05$) and less backwash-ileitis (0% vs 8%;$p<0.03$) than never smokers. Quitters after diagnosis needed more oral steroids (79% vs 55%;$p<0.04$) and hospitalizations (54% vs 32%;$p<0.05$) than quitters before diagnosis. There was no dose-response in CD, but for UC heavy smokers needed less oral and iv steroids (56% vs 88%;$p<0.04$ and 0% vs 35%;$p<0.01$) and hospitalizations (26% vs 59%;$p<0.05$), and had more restriction to the rectum (26% vs 0%;$p<0.03$) than light smokers. Passive smoking CD patients needed more frequently immunosuppressive (68% vs 49%;$p<0.04$) and infliximab (29% vs 11%;$p<0.02$). Passive smoking UC patients had more pouchitis (100% vs 44%;$p<0.04$) and backwash ileitis (16% vs 4%;$p<0.03$). Conclusion: We could not establish a detrimental role of active smoking on CD, but we did show a detrimental effect of passive smoking (use of immunosuppressive and infliximab) on CD. Active smoking and higher daily consumption had beneficial effects (less colectomy, hospitalizations, steroids and PSC) in UC. Although 89% of IBD patients have smoking cessation plans only 11% quit smoking. Tailor made smoking cessation programs and basic research concerning the underlying beneficial molecular mechanism of smoking in UC patients are needed.

**Faecal calprotectin: a non-invasive marker of disease activity in Inflammatory Bowel Disease**

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Calprotectin belongs to a group of calcium-binding proteins in the S100 family. It is found in abundance in neutrophil granulocytes and the presence in stool can be seen as a direct representation of neutrophil migration into the gastrointestinal tract. The aim of this study was to investigate the correlation between faecal calprotectin and disease activity in subjects with inflammatory bowel disease (IBD). Furthermore, we assessed whether the faecal calprotectin concentration could provide a presymptomatic measure of an imminent disease relapse in subjects with Crohn's disease (CD) and ulcerative colitis (UC).Calprotectin was measured using a Time Resolved Immuno assay in stool samples from 153 subjects with IBD (93 with CD and 60 with UC). Simultaneously, disease activity was measured using clinical disease activity indices (CD: Harvey-Bradshaw Index (HBI); UC: Simple Short Colitis Activity Index (SCCAI)). 82 subjects with IBD (43 with CD and 39 with UC) in clinical remission were subsequently followed for a period of 9 months, undergoing regular clinical evaluations. Relapse was defined as an increase in the HBI score to > 4 or in the SCCAI score to > 4 and/or whenever an increase of symptoms sufficient in severity warranted change in treatment.In UC the calprotectin concentration correlated significantly with disease activity (r=0.42, p=0.001). In CD the calprotectin concentration did not correlate with disease activity (r= -0.005, p=0.96). A total of 28 subjects had a relapse over the 9 months period (CD: 14; UC 14). Mean calprotectin values in the relapse group of UC subjects (153.9 mg/l, SD 7.6) differed significantly (p=0.014) from that of the non-relapse group (30 mg/l, SD 6.1). In CD there was no difference (relapse: 132.8 mg/l, SD 7.4; non-relapse 76.5 mg/l, SD 6.2; p=0.37). At 85 mg/l the sensitivity of calprotectin for predicting relapse was 71% and 64% with a specificity of 76% and 52%, respectively for UC and CD.
In conclusion, in UC faecal calprotectin proves to be a promising noninvasive tool for optimizing therapy and patient monitoring. It correlates with disease activity (SSCAI index) and proves to be a predictor of clinical relapse. In CD, however there was no correlation between faecal calprotectin and disease activity (HBI index). Furthermore faecal calprotectin cannot be used as a predictor of relapse as defined by the HBI index suggesting that the latter only partly depends on inflammatory changes.

## Sodium and liquid balance in ileostomy subjects

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After ileostomy, normal colonic function will be lost, resulting in a reduced re-absorption of electrolytes and water. Ileostomy subjects are advised by dieticians in the Netherlands to consume at least 14-15 g (240-257 mmol) of sodium and 2.5 L of liquids per day. However, few data is available on the optimal nutritional advices of sodium and liquids for ileostomy subjects.The objective of the study was to determine the sodium and liquid balance in ileostomy subjects, who are in a clinical good condition and had a stable body weight. Exclusion criteria were ileal resection of >25 cm or ileostomy output of >2 L/d. Seventeen ileostomy subjects (5 male; mean 49 y, range 23-75 y) participated in the study. Subjects consumed a controlled diet for 28 days with ad libitum intake of sodium and water. Salt sachets (4 g) and a standard drinking cup (300 mL) were provided and each consumed salt sachet and finished cup were reported in a diary. The sodium and liquid balance (48 h) was calculated for day 12 and 13 and for day 26 and 27 as the total dietary intake of sodium and liquids (48 h) minus the total excretion of these components (48 h) with ileostomy output, urine, skin (water evaporation assumed to be 500 mL/d and sodium loss 20 mmol/d) and respiratory tract (water evaporation assumed to be 400 mL/d). The mean (± SD) dietary intake of sodium was 207 (34) mmol/d and the mean dietary intake of liquids was 3486 (570) mL/d. The mean water content of the ileostomy output was 815 (332) mL/ 24h and the sodium content in ileostomy output was 80.9 (33) mmol/d. The mean urinary volume was 1634 (523) mL/ 24h and the urinary sodium content was 85 (52) mmol/L. The urinary Na:K ratio was found to be 1.1 (0.6). Based on these findings the mean sodium balance of the subjects was calculated to be 20.8 (47.6) mmol (range -45.9 – 145.9) and the mean liquid balance was 136.7 (729.3) mL (range -902.8 – 1557.0). The mean aldosterone level was 1.3 (0.9) mmol/L (normal for laboratory 0.1-0.7).The overall sodium balance and liquid balance was slightly positive over 48 h probably due to extra attention of the subjects to their dietary behaviour. The present study indicates that the subjects bodies are continuously compensating for the obligatory losses of sodium and liquids, as was shown by elevated serum aldosteron levels and reduced urinary sodium content and Na:K ratio. Our findings indicate that the current Dutch dietary guidelines for ileostomy patients can be maintained.

**Predictive factors of response to cyclosporine and quality-of-life in steroid-refractory ulcerative colitis. A long term follow-up**

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Introduction: Cyclosporine (CSA) has been effective in patients with corticosteroid-refractory ulcerative colitis (UC). We previously reported follow-up data in a large cohort of patients with UC. The aim of this study was to evaluate factors predictive of response to CSA in corticosteroid-resistant UC in a non-referral regional hospital. A quality-of-life (QOL) analysis was conducted in all patients. Methods: A retrospective survey was performed with 69 consecutive patients diagnosed with corticosteroid-refractory UC who were treated with CSA between 1994-2006. Blood CSA levels, full blood count, renal and liver function tests were documented. Medical charts were reviewed for possible side effects and complications of cyclosporine therapy, and survival. QOL was assessed using the Short Form 36 (SF-36) and Dutch Inflammatory Bowel Disease Questionnaire score list (IBDQ). Results: Thirty-five patients (51%) were able to avoid colectomy following successful CSA therapy at 1 year. Overall, 28 of 69 patients (40.6%) had a sustained response after CSA treatment with a median follow-up of 63 ± 36 (9-148) months. The main side-effects during treatment were infections (1.4%), hypertension (6%), elevated liver function tests (2.9%) and reversible renal impairment (12%). A high clinical activity index and pancolitis at admission were associated with a poor initial response to cyclosporine ($p<0.05$). QOL assessment showed comparable results in medical and surgical treated patients.
Conclusion: CSA is an effective and safe alternative to colectomy in severe UC. The use of CSA is further supported by comparable QOL in patients who were treated with CSA to those who underwent colectomy. However, pancolitis on admission is predictive of patients who are unlikely to respond to CSA, and who will require a colectomy.

**Infliximab in paediatric Crohn's disease: long-term follow-up of an unselected cohort***

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The purpose of this study was to describe the clinical experience with the anti-tumor necrosis factor chimeric monoclonal antibody, infliximab, in paediatric patients with Crohn's disease (CD) in The Netherlands. The early stages of immune-mediated disease may be more susceptible to immunomodulation and the natural history of CD may be altered. Therefore, we examined if children had prolonged duration of response when infliximab was initiated early in the disease course. Clinical response and adverse events were recorded for all Dutch paediatric CD patients treated with infliximab from October 1992 to June 2006. Sixty-two CD patients (36 boys) in 9 hospitals were treated with infliximab. Mean age at the start of infliximab therapy was 14.2 years (range, 7.1-18.2 years). Mean follow-up since the start of infliximab was 32 months. In total, 744 infliximab infusions were administered. Analysis of the entire cohort demonstrates that 14.5% of patients had prolonged response, while 59.7% were infliximab dependent and 22.6% lost response. In patients with fistulizing disease prolonged response to infliximab therapy was seen in 50%. In total, 8 patients (12.9%) developed an infection during infliximab therapy and 7 of the 62 patients (11.3%) had an immediate allergic reaction during infusion. There was no statistical difference regarding response to infliximab therapy in the entire cohort when started within 1 or within 2 years after CD was diagnosed as compared to after 1 or after 2 years.This study describes the longest follow-up of a large, unselected paediatric CD cohort receiving repeated infusions of infliximab. Infliximab is a very effective therapy in these children not responding to standard therapies. Clinical response to infliximab therapy is seen in 75% of patients, which is even higher than the response in adult CD patients. It is important to note, however, that 60% of this cohort is dependent on repeated infliximab infusions. There was no difference in response between early and late disease for more or less than both 1 and 2 years interval between diagnosis and start of infliximab. Infliximab maintenance therapy seems very effective and safe in paediatric CD. Long-term safety however, is still of major concern.

## Natalizumab does not require the concomitant use of immunosuppressants or corticosteroids for the induction of sustained response and remission

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Purpose: The concomitant use of immunosuppressants (IMM) was previously shown to be unnecessary to sustain the long-term efficacy of natalizumab in patients who initially responded to natalizumab; corticosteroid (CS) elimination was also possible without concomitant IMM use.1 The subanalysis described below was undertaken to assess the need for concomitant IMM or CS for induction of response or remission with natalizumab. Methods: In the phase 3 ENCORE trial, 509 patients with active disease (Crohn's Disease Activity Index [CDAI] scores ≥220 and  450) and evidence of inflammation (defined as C-reactive protein levels > upper limit of normal [2.87 mg/L]) were randomized 1:1 and received natalizumab (300 mg; n=259) or placebo (n=250) infusions at Weeks 0, 4, and 8. Efficacy and safety were assessed at Weeks 4, 8 and 12. The primary endpoint was the ability of natalizumab to induce a clinical response (≥ 70 point decrease in baseline CDAI score) by Week 8 that was sustained through Week 12. The ENCORE protocol specified that IMM be continued throughout the trial consistent with baseline use. Results: Greater than one-third (37%; 188/509) of the ENCORE patient population were not taking IMM or CS at baseline, and therefore received natalizumab (n=98) or placebo (n=90) without concomitant IMM or CS. The remaining 321 patients received concomitant IMM and/or CS during the trial (natalizumab=169, placebo=152). Overall response and remission rates in the 2 groups of patients were comparable (Table). Sustained response at Weeks 8 and 12 occurred in 51% of –IMM/CS natalizumab– and 31% of –IMM/CS placebo–treated patients (p=0.003). The treatment effect was evident after one infusion (Week 4) and response rates continued to improve at subsequent assessments performed at Weeks 8 and 12.

Conclusions: The induction benefit of natalizumab in the ENCORE trial was comparable in those who used, or did not use concomitant IMM or CS. A significant difference in the proportions of natalizumab-treated patients that achieved response or remission was demonstrated as early as Week 4 in –IMM/CS patients. Response and remission were durable (sustained through Weeks 8 and 12) in natalizumab-treated patients compared with placebo-treated patients regardless of IMM or CS use.

1. Sandborn et al. Gastroenterol. 2006; 130(4 Suppl 2):A482

| | Response | | | | Remission | | | |
|---|---|---|---|---|---|---|---|---|
| | –IMM/CS | | +IMM/CS | | —IMM/CS | | +IMM/CS | |
| | PBO | NAT | PBO | NAT | PBO | NAT | PBO | NAT |
| Week 4 | 36% | 54%[a] | 38% | 50%[b] | 8% | 22%[a] | 20% | 25% |
| Week 8 | 40% | 56%[b] | 40% | 57%[a] | 19% | 28% | 22% | 34%[a] |
| Week 12 | 40% | 62%[a] | 46% | 59%[b] | 22% | 39%[a] | 27% | 37%[b] |
| Weeks 8 & 12 | 31% | 51%[a] | 34% | 46%[b] | 13% | 24%[b] | 18% | 27%[b] |

[a]p≤0.01; [b]p<0.05

**A single centre experience of adalimumab treatment in patients with luminal and fistulizing Crohn's disease (CD): do antibodies to infliximab (ATIs) affect clinical outcome?**

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Infliximab is an effective treatment for CD. However, antibodies to infliximab (ATIs) can lead to allergic reactions or loss of efficacy. Adalimumab is thought to be effective in these patients. However, the effect of ATIs on treatment with adalimumab is still unknown. The aim of this study was to assess the efficacy of adalimumab in patients with luminal or fistulizing CD and to determine whether ATIs affect treatment outcome. Patients with active luminal or fistulizing CD who failed to respond to or were intolerant to infliximab were treated with adalimumab. The following subcutaneous regimen was used: 160 mg at week 0, 80 mg at week 2 and 40 mg every 2 weeks. Clinical response and side effects were assessed. Prior to treatment ATIs were determined in all patients. In total 19 patients were included, the majority was female (16/19) and median age was 36 yrs (range 22-50). 12 patients had luminal CD and 7 had fistulizing CD. Infliximab treatment was stopped due to non-response in 5 patients and due to intolerance to infliximab in 14 patients. Median duration of adalimumab treatment was 156 days (range 30-303). In patients with luminal CD clinical response was 50% (6/12) and in patients with fistulizing CD 85% (6/7). Older age independently predicted non-response (OR=0.81 for a 1-year increase in age, 95% CI: 0.59-0.99, p=0.038). Side effects were seen in 32% of patients (6/19). ATIs were present in 58% of patients (11/19) of which 55% (6/11) were nonresponders and 45% (5/11) developed side effects. The presence of ATIs tended to decrease response rates (p=0.147) and to result in intolerance to adalimumab (p=0.177). Conclusions: Adalimumab is mainly well tolerated and is an effective treatment in CD, particularly for fistulizing CD. Older age is an independent predictor of non-response to adalimumab. Furthermore, the presence of ATIs tended to be associated with non-response and the occurrence of side effects during adalimumab treatment.

## Prenatal exposure to famine and functional bowel disorders

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Prenatal exposure to famine is an intrauterine stressor that is associated with cardiovascular diseases and glucose intolerance (Roseboom et al. Early Hum Dev. 2006). As early life events are accepted as predisposing factor to develop functional bowel disorders (FBD) later in life, we evaluated whether exposure to famine in utero and growth retardation are associated with an increased prevalence of FBD in adulthood.The Dutch Famine Birth Cohort consists of adults born as term singletons in the Netherlands, around the time of the 1944-1945 Dutch famine. Subjects exposed during late, mid and early gestation are compared to non exposed subjects born before or conceived after the Dutch famine. An individual is considered prenatally exposed to famine if the average daily ration for adults during any 13-week period of gestation was less than 1000 calories. Participants were invited to fill out the Rome II questionnaire to evaluate the presence of irritable bowel syndrome or functional dyspepsia.A total of 851 subjects filled out the Rome II criteria. 349 Subjects (41%) were prenatally exposed to famine, 147 (17 %) during late, 123 (15%) during mid and 79 (9%) during early gestation, and were compared to 502 non exposed subjects. The prevalence of FBD in adults with and without prenatal exposure to famine was 13% and 15%, respectively (NS) and was not significantly influenced by exposure during late (11%), mid (15%) or early (14%) gestation. Gastrointestinal symptoms (constipation, diarrhea or abdominal pain) not fulfilling the Rome II criteria for FBD were reported in 18% of the exposed compared to 22% of the non exposed subjects (NS). Birth weight and ponderal index (birth weight/heights x 100) were comparable between controls (3353.1 ± 20.0 g, 26.2 ± 0.1 103g/cm3, respectively) and FBD patients (3356.0 ± 39.0 g, 26.3 ± 0.2 103g/cm3, respectively, NS). This study shows that the 1) prevalence of FBD is not increased in adults exposed to famine during gestation and 2) that there is no relation between low birth weight or ponderal index and FBD. Therefore, we conclude that intrauterine undernutrition or growth retardation are not considered risk factors in developing FBD later in life.

**Additional use of enemas versus conventional treatment in children with severe constipation: a randomized controlled trial***

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Treatment of constipated children is often long-lasting since up to 30% of these children show unsuccessful outcome after 5 years. Conventional treatment consists generally of oral laxatives. Children refractory to oral laxatives may benefit from regular rectal evacuation by enemas.
The aim of this study was to compare clinical effectiveness of additional treatment with enemas (ATE) to conventional treatment (CT) alone in constipated children.
Children aged 8-18 years with at least 2 years symptoms of constipation, as defined by the classic Iowa criteria, were included. Polyethylene glycol was administrated orally to both treatment groups. Children randomized to ATE received additionally 3 enemas/ -week and this frequency was reduced by 1 enema every 3 months. Defecation pattern was assessed at baseline and after one year of treatment. Success was defined as defecation frequency ≥3/week and fecal incontinence frequency <1/week irrespectively of laxative use.
A total of 102 children, 66 male, with a mean age of 11.1±2.1 years, were included and randomized to ATE (n=52) or CT (n=50). Mean duration of symptoms was 7.1±3.0 years. A total of 87 patients completed the study; ATE: n= 44 (85%), CT: n= 43 (86%). After one year of treatment a significant increase in median defecation frequency (ATE: 1.5 vs 5.0/week, p<.001; CT: 1.0 vs 4.5/week, p<.001) and a significant decrease in median fecal incontinence frequency (ATE: 8.0 vs 0.8/week, p<.001; CT: 6.5 vs 0.5/week, p<.001) was found and was not different between treatment groups. Similar success rates after one year of treatment were found for ATE and CT, 41% versus 44%. Time to first success was not different between ATE and CT (p=0.72, log-rank test).
Conclusion: There is no additional effect of enemas compared to oral laxatives alone in the treatment of severely constipated children. Low success rates after one year of treatment indicate that both oral and rectal laxatives are insufficient in treating severe constipation. Development of new compounds for childhood constipation is needed.

**Enhanced expression of genes associated with visceral hypersensitivity in the small intestine of Irritable Bowel Syndrome patients**

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Visceral hypersensitivity of the colorectal and small intestinal region has been demonstrated in irritable bowel syndrome (IBS) patients. An increased serine protease activity was found in colonic mucosa of IBS patients. Moreover, IBS mucosal supernatant-induced hyperalgesia to colorectal distension was diminished after preincubation with a serine protease inhibitor. The serine protease trypsin IV, an agonist of protease activated receptor (PAR)-2, may be involved. Increased PAR-2 expression and/or activation promotes hyperalgesia. Furthermore, alterations in serotonergic system components that increase serotonin (5-HT) availability may underlie visceral hypersensitivity. Abnormal mucosal 5-HT content and altered expression of tryptophan hydroxylase (TPH)-1, rate-limiting enzyme in 5-HT biosynthetic pathway, and the specific 5-HT transporter (SERT) in rectal biopsies of IBS patients have been reported. We aimed to determine mucosal serine protease and serotonergic system components in small intestine of IBS patients.Duodenal mucosal biopsies of 34 IBS patients (10 constipation predominant (IBS-C), 11 diarrhea predominant (IBS-D), and 13 alternating IBS patients) and 20 healthy subjects (HS) were collected. Transcript levels of trypsinogen IV, the inactive form of trypsin IV, PAR-2, TPH-1, SERT and several 5-HT3 receptor subunits were quantified by real-time PCR. For normalization PBGD and GAPDH were measured. Furthermore 5-HT content was determined by ELISA. IBS patients showed 1.5-fold higher trypsinogen IV mRNA level, normalized against PBGD, compared to HS (P=0.003). For the subgroups of IBS-D and IBS-C the relative increase was 1.8-fold compared to HS (P=0.010 and P=0.016 respectively). SERT expression, normalized against PBGD, was 1.9-fold higher in IBS patients compared to HS (P=0.010). Increased expression of trypsinogen IV and SERT in IBS patients was confirmed using GAPDH for normalization. Mucosal 5-HT content was 1.7-fold higher in IBS patients compared to HS (P=0.015). The relative increase was 2.1-fold in IBS-C patients compared to HS (P=0.018). Transcript levels of PAR-2, TPH-1 and 5-HT3 receptor subunits did not differ between IBS patients and HS.Conclusions: Enhanced trypsinogen IV expression in IBS may cause increased PAR-2 activation. Increased SERT expression and mucosal 5-HT content in IBS patients suggest higher 5-HT availability. Both are likely to contribute to small intestinal visceral hypersensitivity in IBS patients.

## The mode of delivery in females with Crohn's disease

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In Crohn's disease, perianal fistulae will develop in up to one third of patients. For females in the reproductive years, this could be a problem when giving birth to a child. Studies about perianal disease and delivery mode are scarce and small numbered. Elective caesarean section (CS) is frequently recommended in women with Crohn's disease. In this study we examined the rate of CS with respect to disease characteristics and the effects of the mode of delivery on the course of Crohn's disease.Methods: Females aged 18-80 years with Crohn's disease from our IBD and obstetric databases were eligible for the study. A questionnaire was sent which contained questions about disease characteristics and the current situation. In case of a positive history for pregnancies, a second part contained questions about the pregnancies and the course of Crohn's disease. After 3 months, a reminder was sent to non-responders. Data obtained where collected in a database and SPSS software version 12.0 was used for analysis.Results: From 398 questionnaires, 307 patients responded (77%), but 7 patients gave no further consent for different reasons. Therefore, 300 questionnaires were analysed. At time of the study, 95 (32%) women had never been pregnant, 53 were diagnosed with Crohn's disease after their latest pregnancy and 152 (51%) had at least one pregnancy after the diagnosis of Crohn's disease. Questionnaires were complete in 140 of 152 women with a positive history for pregnancies during Crohn's disease. From these 140 women the first reported pregnancy was analysed and 24 of them (17%) reported active symptoms of Crohn's disease at the onset of pregnancy. In total 43 CS (31%) were performed and 25 of the CS were preventive advises. In the 61 patients known with fistulae, the rate of CS was 44%. In 27 of 97 patients with vaginal deliveries a forceps of vacuum was needed and in 67 patients an episiotomy was performed. Within 6 weeks after delivery, 23 patients (16%) had increased abdominal symptoms without significant differences between the mode of delivery. In 3/97 females (3%) worsening of fistulizing disease was reported after vaginal delivery compared with 5/43 females (12%) after CS.Conclusion: Caesarean section in Crohn's disease is more frequent compared with numbers from the general population in the Netherlands and even more frequent in fistulizing disease. After vaginal delivery, only 3% of females reported worsening of fistulae.

**Involvement of polarity protein LKB1, STRAD and the MARK kinases in Peutz-Jeghers Syndrome**
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Peutz-Jeghers Syndrome (PJS) is a rare autosomal dominant cancer predisposition syndrome caused by loss of the tumor suppressor gene *LKB1*. The family of Par proteins to which LKB1 and its evolutionary homologue Par4 belong, is conserved during evolution. The six members of this family regulate epithelial polarity in *Drosophila*, *C.elegans* and vertebrates by involvement in cell migration and the establishment of the anterior-posterior axis. Furthermore, LKB1 induces cell polarization of single intestinal cells after its activation by adaptor protein STRAD. Also a role in energy metabolism has been proposed, since LKB1 interacted with and activated the AMPK related kinases. Among the *AMPK*-related genes are the *MARK* genes, of which *MARK3* is the *Par1* homologue. Par1 is involved in both the Wnt and Planar Cell Polarity (PCP) signalling pathways. It has been suggested that Par1 phosphorylates dLKB1 to establish anterior-posterior embryonic polarity in *Drosophila* and, in cell lines endogenous LKB1 directs Par1A phosphorylation. More insight in the role of LKB1 in PCP signalling will elucidate the polarity function of LKB1. *LKB1* germline mutations are identified in the majority (about 80%) but not in all patients. Therefore defects in another gene or so far unidentified ways of *LKB1* inactivation may cause PJS. *STRAD* and the *MARK* genes are interesting candidates for the second PJS gene. *LKB1* germline mutation analysis was performed in 21 different PJS families using direct sequencing. In PJS patients without *LKB1* mutations a Multiplex Ligation-dependent Probe Amplification analysis was performed to screen for deletions. In 8 PJS patients without *LKB1* inactivating mutations, *STRAD*, *MARK1*, *MARK2*, *MARK3* and *MARK4* were sequenced. Furthermore, the involvement of STRAD in 42 PJS associated tumors (sporadic lung, colon, gastric and ovarian adenocarcinomas) was studied using loss of heterozygosity (LOH) analysis of 8 markers on chromosome 17, including *TP53*, *BRCA1* and *STRAD* markers. When specific loss of *STRAD* was found, the *STRAD* gene was sequenced to search for mutations. In 19 of 21 (90%) PJS patients *LKB1* was inactivated, of these 2 patients showed *LKB1* exonic losses. No germline mutations in *STRAD* or the *MARK* genes were identified in PJS patients without *LKB1* mutation. Interestingly, of the 42 sporadic adenocarcinomas 45% of informative cases showed loss of the marker near the *STRAD* locus. Specific LOH of the *STRAD* marker was found in 14% of the informative cases. For these patients the *STRAD* gene was sequenced, but no somatic mutations were identified. Despite the frequent occurrence of LOH in the *STRAD* region, our results indicate that inactivation of the *STRAD* gene is not essential in the sporadic adenocarcinomas studied. To conclude, we did not identify a second PJS gene.

Other mechanisms of inactivation of *LKB1* or as yet unidentified intronic *LKB1* mutations possibly creating cryptic splice sites may be the cause of PJS in the remaining families. We speculate, therefore, that the existence of a second PJS locus can be excluded. In our search to unravel the polarity function of LKB1 we identified an interaction between LKB1 and one of the PCP proteins, and this interaction was abolished with LKB1 mutants as found in PJS patients. We therefore propose that inactivation of the polarity function of LKB1 underlies PJS.

## Effect of sildenafil on gastric function assessed with Magnetic Resonance Imaging

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Previous barostat studies have shown that gastric accommodation consists of an adaptive relaxation of the stomach larger than the volume of the meal provided. However, measured with Magnetic Resonance Imaging adaptive relaxation consists solely of an adaptation equal to the volume of the meal provided. Sildenafil, known for its smooth muscle relaxing effect, has been shown to enhance adaptive relaxation when measured with the barostat. Aim of our randomized single blind placebo controlled study was to evaluate the effect of sildenafil on gastric emptying, gastric accommodation and meal distribution measured with MRI. Twelve healthy subjects (two men; mean age 21.3 years; BMI 23 ± 3 kg m-2) participated in two experiments performed on separate days. MRI was used to measure momentary volumes prior to administration of sildenafil 50 mg or placebo orally. Starting 30 min prior to meal ingestion volumes were acquired every 5 min up until 90 min and at 120, 180 and 240 min. The meal (205 kcal) consisted of a scrambled egg, two slices of bread and margarine. At the start of the experiment fasting stomach volumes did not differ significantly between the sildenafil and placebo experiment. After meal ingestion stomach volume and contents volume did not differ significantly between the sildenafil and placebo experiment; 251 ± 48 vs 266 ± 30 ml resp. for the stomach volume and 182 ± 29 vs 195 ± 20 ml resp. for the contents volume. Throughout the experiment stomach volume and contents volume were significantly higher for the sildenafil experiment compared with placebo; mean difference of 16 ml [9-24] for the stomach volume and 13 ml [7-18] for the contents volume. This was not due to a difference in gastric emptying rate between the sildenafil and placebo experiment; 0.64 ± 0.25 vs 0.77 ± 0.11 ml min-1 resp. After meal ingestion air volume increased significantly in the sildenafil and placebo experiment; 69 ± 34 vs 71 ± 23 ml resp. Throughout the experiment air volume did not differ significantly between the experiments. Proximal gastric contents volumes were significantly larger throughout the sildenafil experiment compared with placebo, whereas distal gastric contents did not differ between the experiments.
We conclude that measured with MRI, and under physiological conditions, sildenafil does not induce an increased gastric accommodation response. Moreover, sildenafil does not influence the rate of gastric emptying, but does influence intragastric meal distribution.

**The role of proximal gastric volume in spatial separation of diaphragm and lower esophageal sphincter in GERD patients and controls**

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Spatial separation of the diaphragm and lower esophageal sphincter (LES) occurs frequently in patients with a sliding hiatus hernia and favors gastroesophageal reflux. Although fundic accommodation is associated with a lower basal LES pressure, its effect on esophagogastric junction configuration and hiatal hernia is unknown. Therefore, the aim of this study was to investigate of the relationship between proximal gastric volume, the presence of a double high pressure zone (HPZ) (non-reduced hernia) or a single HPZ (reduced hernia) at the EGJ and acid reflux.Twenty GERD patients (12 men, 8 women) were studied and compared to 20 healthy controls (10 men, 10 women). High-resolution manometry and pH recording was performed for 1 hour before and 2 hours following meal ingestion (500 mL/300 kcal). Volume of the proximal stomach was assessed with three-dimensional ultrasonography before and every 15 minutes after meal ingestion. During fasting, the double HPZ (non-reduced hernia) was present for 31.9 +/- 4.9 minutes/h (53.2%) in GERD patients, and 8.7 +/- 3.3 minutes/h (14.5%) in controls (P<.001). In GERD patients, the presence of non-reduced hernia (double HPZ) fell during the first postprandial hour to 15.9 +/- 4.2 minutes/h, 26.5%, P<.01 whilst this phenomenon was not observed in controls. The rate of transition between the 2 profiles was 5.7 +/- 1.1 per hour in GERD patients and 2.5 +/- 1.0. per hour in controls (P<.001). The pre- and postprandial reflux rate in GERD patients during double HPZ (6.4 +/- 1.1/hr and 18.4 +/- 4.3/hr resp.) was significantly higher than during single HPZ (2.1 +/- 0.6/hr; P<.05 and 3.8 +/- 0.9/hr; P<.05). A similar difference was found in controls. Furthermore, an inverse correlation was found between fundic volume and the time the non-reduced hernia state was present (r=-0.45; P<.05) in GERD patients, but not in controls. Conclusions: 1. In GERD patients the majority of reflux occurs during the hernia state. 2. A postprandial increase in proximal gastric volume is related to a decrease in hernia prevalence.

**Central activation of the cholinergic anti-inflammatory pathway reduces post-operative ileus in mice**

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Introduction: Electrical vagal nerve stimulation activates the cholinergic anti-inflammatory pathway reducing the manipulation induced intestinal muscle inflammation hereby shortening postoperative ileus in mice. Previous studies in a sepsis model showed that this pathway can be activated pharmacologically by central administration of semapimod, a p38 MAPKinase inhibitor formally known as CNI-1493.
Aim: To evaluate the effect of semapimod i.c.v. on intestinal inflammation and the subsequent postoperative ileus in mice.
Methods: Mice underwent a laparotomy (L) or intestinal manipulation (IM) 1h after pre-treatment with 1μg/kg semapimod or saline i.c.v. Drugs were administered through a cannula placed in the right lateral ventricle one week prior to the experiments. 24h after surgery, gastric emptying for semi-liquids was measured using scintigraphy. Inflammation was assessed by MPO-positive cell count in ileal muscle wholemounts. Experiments were repeated 30min after subdiaphragmal vagotomy to assess vagal nerve dependency of this anti-inflammatory mechanism. Values are depicted as mean ± s.e.m. $P<0.05$ was considered statistically significant. Results: IM significantly delayed gastric emptying 24h after surgery in saline treated animals (gastric retention at 80min (RT80) L=3±1%, vs. IM 19±4%, $p<0.05$, n=8) and was associated with inflammation of the manipulated intestine (MPO-pos. cells/mm$^2$: L= 48±7 vs. IM= 381±27, $p<0.05$, n=8). I.c.v. semapimod reduced this intestinal inflammation and improved gastric emptying (MPO-pos. cell/mm$^2$: 227±28, $p<0.05$; RT80: 5±1%, $p<0.05$, n=8). Vagotomy increased IM induced inflammatoin and abolished the effect of semapimod i.c.v. (MPO-pos.cell/mm$^2$: vagotomy-saline 540±78 vs. saline, n=8, $p<0.05$ and vs. vagotomy-semapimod 440±34, n=8, p=0.2).
Conclusion: Our findings show that central application of semapimod reduces manipulation induced intestinal inflammation and shortens POI in mice by means of the vagus nerve. From these data we conclude that the anti-inflammatory effect of i.c.v. semapimod is mediated by activation of the cholinergic anti-inflammatory pathway. Experiments are ongoing identifying the brain nuclei and neurons activated by semapimod.

**Predicting factors for repeated pneumatic balloon dilatation in patients with primary achalasia**

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Background and aim: Pneumatic balloon dilatation (PD) is a regular treatment modality for achalasia patients. The reported success rates of PD vary. Recurrence of symptoms often requires repeated PD. Aim of this study was to identify predicting factors for symptom recurrence requiring repeated PD in patients with primary achalasia. Methods: 391 patients with primary achalasia (M/F 194/197, mean age 50.6 years) treated with PD between 1974 and 2006 were included in this longitudinal cohort study. Baseline PD was performed on 3 consecutive days with balloons of either the same diameter (40 mm), or incremental (30, 35, and 40 mm) diameter all inflated to a pressure of 300 mm Hg for 1 minute. Recurrence of achalasia was defined as symptom recurrence (dysphagia, regurgitation and weight loss) in combination with increased lower esophageal sphincter (LES) pressure on manometry, requiring repeated PD. Patient's characteristics (age at presentation, gender), results of timed barium esophagram and manometry before treatment, as well as PD balloon characteristics (consistent vs incremental diameter and (in)complete obliteration of the balloon's waist during PD) were evaluated as predictors for disease recurrence. Results: 117 patients (29.9 %) underwent repeated PD after a mean follow-up of 46.5 months (range 1-288). The mean age of patients requiring repeated PD was significantly lower than the age of patients without recurrence (43.2 vs 54.2 years, $p < 0.001$). Furthermore, incomplete obliteration of the balloon's waist during baseline PD was associated with a higher chance of disease recurrence during follow-up (recurrence in incomplete vs complete obliteration group 50.8 vs 19.9 %, $p < 0.001$). Recurrence in the incomplete obliteration group also occurred earlier (after mean 39.4 months vs 58.4 months in the complete obliteration group, $p = 0.06$). No differences between groups were found regarding gender ($p= 0.66$), presence of mouse-tail and/or esophagus dilatation on the timed barium esophagram before treatment ($p=0.48$ and $p=0.52$, respectively), LES pressure ($p=0.54$), absence of LES relaxation before treatment ($p= 0.89$) or balloon diameter ($p= 0.73$). Conclusion: In patients with primary achalasia, young age at presentation and incomplete obliteration of the balloon's waist during PD are predicting factors for the need of repeated PD during follow-up. These factors should be taking into account in the follow-up strategy of achalasia patients.

## Involvement of TRPV1 in visceral hypersensitivity to distension in the rat

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50-60% of patients with the irritable bowel syndrome has an increased sensitivity to colonic distension. As studies in TRPV1 knockout mice have shown involvement of TRPV1 in mechanoperception, we evaluated its role in visceral hypersensitivity to distension in 2 different animal models. Visceral hypersensitivity was induced by intracolonic instillation of capsaicine (0.1%) in nonhandled (NH) rats or by acute stress (water avoidance, WA) in maternal separated (MS) Long Evans rats. Visceral sensitivity was assessed by recording of the visceromotor response (VMR) before and after capsaicine or WA. The TRPV1-antagonist capsazepine (10mg/kg, i.p.) or vehicle was administered 30 minutes prior to the second distension protocol. The relative response to colonic distension was calculated by setting the maximum value of the first distension protocol at 100%. Statistical differences were calculated by Wilcoxon signed ranks. In addition, dorsal root ganglia (DRG) of vehicle-treated NH and MS rats were evaluated for in situ TRPV1 expression. Our results show that intracolonic capsaicine, but not vehicle alone induces an enhanced VMR to distension (n=7, 173.9+/-18.9% P=0.018 and 114.8+/-8.2% respectively). Similarly, WA results in an enhanced VMR in MS but not in NH rats (n=10, 145.3+/-11.4% P=0.004 and 95.4+/-8.2%). In the intraluminal capsaicine as well as in the acute-stress model, visceral hypersensitivity was inhibited by capsazepine treatment (n=7, 100.5+/-8.9% and 97.5+/-5.7%), but not by vehicle alone (n=7, 171.9+/-43.5% P=0.028 and 136.1+/-7.9% P=0.043). There was no increase in the % of TRPV1 expressing neurons when comparing DRG of post-WA MS and NH animals. Conclusions: The present data indicate 1) that direct TRPV1 activation leads to enhanced visceral sensitivity to distension, and 2) that visceral hypersensitivity to distention, when induced by stress in the maternal separation model, is mediated by TRPV1. In the latter, this increase in visceral sensitivity is not related to enhanced numbers of TRPV1-expressing DRG-neurons. These data suggest that TRPV1 is an important mediator in visceral hypersensitivity and is a potential target to treat IBS patients with visceral hypersensitivity.

## Safety and Efficacy of Tegaserod in Children*

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Background: Tegaserod is increasingly prescribed by pediatric gastroenterologists although there are very few published data concerning its use in children. Aim: To assess the efficacy and safety of tegaserod in children. Methods: Patients treated with tegaserod in our Division from 2004 to 2006 were retrospectively evaluated and interviewed. Defecation and fecal incontinence frequency, and global assessment score of relief of symptoms were assessed. Results: 72 children (44 girls) were evaluated. Median age at initiation of tegaserod was 9.6 (range, 1.1-18.3) yrs, median duration of symptoms 5.4 (range, 0.1-15.6) yrs and median follow up time after initiation of tegaserod 10.6 (range, 0.1-45.2) months. Indications to prescribe tegaserod were constipation (61%) and functional abdominal pain syndromes such as functional dyspepsia or IBS (39%). Defecation frequency was lower in the constipated group than in the non constipated group (1 vs. 5/wk, $p=0.04$) and increased after tegaserod use (1 vs.7/wk, $p<0.001$) whereas it did not change in the other group. Fecal incontinence decreased during treatment (45% vs. 23%, $p<0.001$). Parents rated global assessment score of relief of constipation after tegaserod use as moderate or significant in 74% of the constipated group and 69% in the other group. Relief of abdominal pain and bloating symptoms after tegaserod was rated as moderate or significant in 67% and 63% of all cases in the constipated group, respectively. In the group with functional abdominal pain syndromes moderate or significant relief for abdominal pain and bloating symptoms was seen in 60% and 67% of the patients, respectively. In children older than 8 yrs, 81% experienced moderate or significant relief for their main complaint after tegaserod vs. 57% of the younger group ($p=0.03$).The median dose of tegaserod prescribed was 0.22 (range, 0.05-0.87) mg/kg/day. Adverse events were observed in 34% of the patients. The most common side effects consisted of mild, self-limiting diarrhea (20%) and abdominal pain (10%). Tegaserod had been discontinued by 14 (19%) of the study children, 7 in the constipated group and 7 in the other group, at time of the interview. Poor therapeutic response was the main reason (8.3%), followed by no longer needing the medication in 5.6% of all cases. Only one patient discontinued tegaserod because of side effects; she experienced pain at the cecostomy site. Conclusion: Tegaserod can be safely used in children of different ages and effectively relieves a variety of functional gastrointestinal symptoms. Further randomized placebo-controlled studies are needed to support evidence-based pediatric prescribing of tegaserod.

**Mast cell stabilization as treatment of post-operative ileus: a clinical proof of principle study**

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Background: Postoperative ileus in mice is mediated by intestinal inflammation resulting from handling-induced mast cell activation. Therefore, mast cell stabilization may represent a new therapeutic approach to shorten postoperative ileus. Aim: To study the effect of ketotifen, a mast cell stabilizer, on postoperative gastrointestinal transit. Methods: In this pilot study, 60 patients (age 27-77yrs) undergoing major abdominal surgery for gynaecological malignancy were randomized (double blinded) to treatment with ketotifen (4 or 12mg) or placebo. Patients were treated for 6 days starting 3 days prior to surgery. Gastric emptying for liquids and colonic transit were measured at 24, 48 and 72hrs after surgery using scinitgraphy. Colonic transit was represented as geometrical centre of activity (segment 1= cecum to 7= stool). Gastric retention (1hr after intake of 40ml radiolabeled H2O) 24hr after surgery was selected as primary outcome. Secondary endpoints were colonic transit and abdominal symptoms. Data are expressed as median (interquartile range) and $p<0.05$ was considered statistically significant. Results: Gastric retention 1hr after liquid intake was significantly reduced by 12mg (median 3% (1-7), $p=0.01$), but not by 4mg ketotifen (18% (3-45), $p=0.6$) compared to placebo (16% (5-75)). The 48-72hr post-surgical colonic transit in placebo was 0.8 (0.0-1.1) vs. 1.2 (0.2-1.4) colon segments in 12 mg ketotifen group ($p=0.07$). Abdominal cramps improved significantly in patients treated with 12mg ketotifen, whereas time to first flatus, bowel movement, solid food intake and ready for discharge were not affected. Conclusion: Ketotifen significantly improves gastric emptying and showed a tendency to improvement of colonic transit after abdominal surgery. These results warrant further exploration of mast cell stabilizers as putative therapy for postoperative ileus.

**Serotonin receptor 3A polymorphism C178T is associated with visceral hypersensitivity in GERD patients**

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Familial clustering and twin studies show that susceptibility to gastroesophageal reflux disease (GERD) has a hereditary component. Many GERD patients display visceral hypersensitivity of the esophagus. Serotonin (5-HT) plays an important role in the development of visceral hypersensitivity. 5-HT reuptake inhibiting drugs diminish esophageal hypersensitivity, possibly by increasing the availability of 5-HT to the descending antinociceptive pathways. 5-HT3 receptors play a role in this signaling pathway.
The T-allele of the C178T SNP in the HTR3A gene results in enhanced translation of the 5-HT3A receptor subunit. The affinity of the 5-HT3A subunit for 5-HT is lower than 5-HT3B, and 5-HT3 receptors containing 5-HT3A desensitize more rapidly. 5-HT-driven activity in the amygdala and prefrontal cortices is different in subjects with CC or CT.
We aimed to investigate the relation between HTR3A C178T and disease susceptibility and visceral hypersensitivity in GERD.
GERD was defined as having pathological acid exposure on 24-hour esophageal pH-monitoring combined with symptom association scores (total time pH<4 ≥6% or SI≥50% or SAP≥95%). Visceral hypersensitivity was then defined as total reflux time <6% (physiological) combined with positive symptom association scores. DNA was extracted from blood from 320 GERD patients (189 male, mean age 48.7, mean BMI 26) and 339 symptom-free controls (95 male, mean age 41.5, mean BMI 24). Genotyping of HTR3A C178T was done by molecular beacon assay.
Genotype distribution is displayed in the attached table.
HTR3A C178T was not associated with GERD as a whole but GERD characterized by physiological reflux time and positive symptom association was associated: logistic regression with age, sex and BMI as covariates yielded an odds ratio of 1.86 (95%CI 1.05 – 3.28; P = 0.033). When the group of GERD patients with pathological reflux was dichotomized according to positive SAP, no differences in genotype distribution were observed.
Conclusions: In viscerally hypersensitive GERD patients HTR3A C178T is more prevalent. In these patients, decreased affinity for 5-HT by overexpressed 5-HT3A receptor subunits, and subsequent acceleration of desensitization could cause their visceral hypersensitivity.

**Localized distension of the esophagogastric junction augments triggering of TLESRs in healthy volunteers: A novel neuroregulatory mechanism***

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Transient lower esophageal sphincter relaxation (TLESR) is the major mechanism of gastroesophageal reflux (GER) and stimulation of gastric mechanoreceptors is the only characterized mechanism initiating the TLESR reflex. Placement of catheters across the esophagogastric junction (EGJ) is known to increase GER triggering, suggestive of the presence of additional sensory mechanisms localized to the EGJ that are sensitive to distension and may influence the TLESR reflex. In this study we explored the possible existence of such a mechanism. An esophageal manometric catheter incorporating an 8cm internal balloon adjacent to a sleeve sensor was developed to enable continuous recording of LES pressure during balloon distension of the EGJ. Inflation of the balloon doubled the cross-section of the trans-sphincteric portion of the catheter from 4mm OD to 4x10mm OD. Two studies were performed in healthy subjects who were asked to consume either 600ml of Coca Cola® (Study 1, n=10) or a 'refluxogenic meal' consisting of a hamburger, French fries and 300ml of orange juice (Study 2, n=8). STUDY 1: After catheter placement, a 30 min adaptation period was allowed before the EGJ was distended or left undistended (randomized). A 45 min baseline recording was made. The subjects then consumed soft drink and 1hr later the EGJ distension status was reversed. The baseline recording, consumption of soft drink and post-drink recordings were then repeated. On a separate day the protocol was repeated with the order of EGJ distension reversed. STUDY 2: After catheter placement, 30 min of adaptation and 45 min baseline recordings, subjects consumed the meal and recordings were made for a further 3hrs. A repeat study was performed on a separate day with EGJ distension status reversed. EGJ distension was not perceived. In study 1, more TLESRs were triggered during the post prandial period with the EGJ distended compared to when not distended(9.5(8.0;11.5) vs 8.0(6.0;11.0) respectively, p=0.042).
This effect was more pronounced in the post prandial period in study 2 (distended: 22.0(18.0;29.0) vs not distended: 15.5(13.0;26.0)TLESRs). Localized EGJ distension augments triggering of TLESRs suggesting that vagal tension receptors localized to the EGJ play a role in the neuroregulation of the TLESR reflex. Such a mechanism may underlie the increased GER triggering seen in association with the increased EGJ distensibility previously characterized in patients with GERD and/or hiatus hernia

**The gastroesophageal pressure gradient in GERD, relationships with obesity and hiatal hernia**

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From previous studies it is clear that hiatal hernia (HH) and the gastroesophageal pressure gradient (GEPG) both play a role in the pathophysiology of gastroesophageal reflux disease (GERD). However, until now no data of the combined effect of BMI, GEPG and HH is available for large groups of GERD patients. 154 symptomatic patients with pathologic reflux (pH<4 ≥ 6% of time) and/or positive symptom association (SI≥50;SAP≥95) on 24-hour pH-metry were included. All patients underwent stationary esophageal manometry. Mean intragastric and distal intra-esophageal pressures were determined during peak inspiration and mid-expiration. GEPG was defined as mean intragastric pressure minus mean intra-esophageal pressure. Presence of hiatal hernia (HH) or esophagitis was assessed endoscopically.
Presence of HH was strongly associated with being overweight (BMI>25) (P=.009) and the presence of esophagitis (P<.0005). Patients with HH had higher inspiratory intra-gastric pressure (1.79 vs. 1.58 kPa; P=.016) and inspiratory and expiratory GEPG (1.59 vs. 1.19 kPa; P<.0005 and 0.41 vs. 0.11 kPa; P=.001, respectively). In patients without HH, BMI was correlated with inspiratory and expiratory intra-gastric pressure (r 0.45 and r 0.46, respectively, P≤.002). In the presence of HH these correlations were weaker (r 0.29 and r 0.33, respectively, P≤.002) but in this group BMI correlated with expiratory intra-esophageal pressure (r 0.28, P=.003) and inspiratory GEPG (r 0.20, P=.036). In both groups inspiratory GEPGs correlated with intra-gastric pressure (no HH r 0.38, HH r 0.43; P≤.01) but a much stronger correlation was seen with intra-esophageal pressure; in the group with HH this was less pronounced (r-0.81 vs. r-0.59; all P<.0005). Expiratory GEPGs were strongly correlated with intra-esophageal pressure, less pronounced, again, in the HH group (r-0.80 vs. r-0.69; all P<.0005); intra-gastric pressure and GEPG did not correlate at all.
Conclusions: Overweight GERD patients more often have HH and have increased intra-gastric pressure. In the absence of HH, GEPG variance is determined almost exclusively by the intra-esophageal pressure, but in the presence of HH both intra-gastric and intra-esophageal pressure are determinants of the GEPG. It stands to reason that the effects of HH and elevated intra-gastric pressure act synergistically in the etiology of GERD in the obese.

**Fundoplication reduces gastroesophageal reflux in a refluxate-dependent manner**

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Fundoplication almost abolishes acid reflux, but the effect of the procedure on non-acid and gas reflux has not been studied extensively. Symptoms after surgery are often attributed to the inability of venting air from the stomach, but this has not been tested in an ambulatory setting.Prior to surgery, stationary impedance-pH measurements were performed for 20-min after reflux provocation by intragastric inflation of 600 mL of air. This was followed by ambulatory 24-hr impedance-pH measurements. The incidence of air swallowing, gas reflux, acidic and weakly acidic reflux was assessed. Measurements were repeated 3 months after fundoplication. In the stationary study fundoplication greatly reduced the occurrence of liquid (from 0.7±0.3 to 0.0±0.0, $p<0.01$), mixed (from 1.4±0.5 to 0.0±0.0, $p<0.01$) and pure gas reflux events (from 2.6±0.5 to 0.8±0.4, $p<0.01$) after air inflation. In the ambulatory study, there was a large decrease in the prevalence of both acidic (-97%, from 47.7±6.2 to 1.6±0.5, $p<0.01$) and weakly acidic reflux (-90%, from 24.7±9.9 to 2.6±1.0, $p<0.01$). The decrease in gas reflux was less pronounced, albeit statistically significant (-51%, from 24.3±5.1 to 11.8±3.1, $p<0.01$). There was a larger decrease in reflux events reaching the proximal esophagus (-99%, from 16.5±4.5 to 0.1±0.1, $p<0.01$) than in events reaching the distal esophagus (-79%, from 11.4±1.6 to 2.4±0.8, $p<0.01$). Fundoplication significantly decreased both volume and acid clearance time (from 18.1±1.5 to 15.6±1.4 s, $p<0.05$ and from 119.9±22.3 to 18.2±6.2 s, $p<0.01$). In 4 patients no acidic or weakly acidic reflux was found at all after the operation and in 1 patient there was also a total inhibition of pure gas reflux. Differences between patients of self-reported presence and severity of bloating, inability to belch and inability to vomit were not related to differences in air swallowing or reflux occurrence of gas and liquid during the stationary and ambulatory study.
Conclusions: 1: Fundoplication reduces both acidic and weakly acidic reflux and also pure gas reflux, in some patients reflux is blocked entirely. 2: The reduction in liquid-containing (acidic and weakly acidic) reflux is larger than the reduction in pure gas reflux. 3: The pronounced reduction in proximal reflux episodes and of acid and volume clearance time suggests a reduction in volume of reflux episodes after surgery. 4: Symptoms after fundoplication can not be predicted by objective findings.

**Neuroregulation of the TLESR reflex by sensory mechanisms sensitive to luminal contents at the esophago-gastric junction: A study in neonates with adult implications***

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Gastric distension stimulates tension receptors and hence triggers the vago-vagal transient lower esophageal sphincter relaxation(TLESR) reflex causing TLESRs and gastroesophageal reflux(GER). Despite faster gastric emptying, infants in the right lateral position(RLP) trigger more TLESRs and GER when compared to the left lateral position(LLP). We hypothesized that pooling of milk at the level of the esophago-gastric junction(EGJ) augments triggering of TLESRs. Seven healthy infants (3 male, post menstrual age: 36(35-37)weeks) were studied twice using an esophageal impedance-manometry catheter incorporating a feeding tube. After tube placement with the infusion port of the catheter 2.5cm distal to the midpoint of the lower esophageal sphincter, infants were randomly positioned either at their RLP or LLP. They were then tube fed their normal feed (65(40-75)ml) at a constant infusion rate of 160ml/hr. Recordings were made during the feed and 15 min thereafter. The next day, the study was repeated with the infant in the opposite position. In the RLP, the time from the start of infusion to the triggering of the first TLESR was significantly shorter than when infants were on the LLP(271±205sec vs 502±79sec respectively, p=0.01) meaning that volume of feed required to meet the threshold for initiation of the TLESR reflex was also significantly lower(12.0±9.1ml vs 22.3±3.5ml respectively, p=0.01). Under these standardized feed infusion conditions more TLESRs and liquid GER episodes were triggered in the RLP compared to LLP(4.6±1.5 vs 2.3±1.5, $p<0.01$ & 4.1±1.7 vs 1.7±1.7, $p<0.05$ respectively). Gas and mixed GER episodes were rarely seen in both positions. Therefore the difference in liquid GER triggering was not related to change in reflux type. In the RLP, TLESRs and reflux are triggered earlier after the commencement of feed infusion and more frequently during the feed overall. In this experimental paradigm the rate of gastric distension was assumed to be similar in both positions by virtue of the volume, rate and type of feed infused being kept constant. These findings provide clear evidence for the presence of mechanisms for luminal sensing of gastric contents at the level of EGJ which regulate the threshold for triggering of the TLESR reflex by gastric distension. Such mechanisms have yet to be described but are likely to involve vagal mucosal receptors localized to the EGJ and may prove to be a novel target for therapeutic interventions.

## Butyrate modulates oxidative stress in the colonic mucosa of healthy humans

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Butyrate, produced by colonic microbial fermentation, is the prime energy substrate for colonocytes. In addition, it has an anti-carcinogenic potential and is suggested to inhibit inflammation. Cancer and inflammation are associated with oxidative stress to the mucosa. In vitro studies showed that butyrate increased glutathione-S-transferase (GST) activity and reduced $H^2O^2$-induced DNA damage, suggesting a role for butyrate on oxidative stress. Therefore, the effect of butyrate on several parameters of oxidative damage and anti-oxidant defense were studied in the colon of healthy human volunteers. A randomized, double blind, placebo controlled, crossover study was performed in 16 healthy volunteers. Treatments consisted of daily rectal administration of a 60 ml enema containing 100 mM sodium-butyrate or placebo (saline) for two weeks with a two weeks wash-out period. After each treatment, biopsies were taken from the sigmoid colon. Non-protein trolox equivalent antioxidant capacity (TEAC), uric acid (UA), reduced glutathione (GSH) and oxidized glutathione (GSSG) levels and the enzyme activity of GST were determined. Malondialdehyde (MDA) was measured as a parameter of lipid peroxidation and the GSH/GSSG ratio was calculated as a marker of oxidative stress. Butyrate resulted in significantly higher ($p<0.05$) GSH (26.5 (20.4-35.2) vs. 22.9 (12.0-31.5) nmol/mg protein), and in lower ($p<0.01$) UA (2.4 (1.6-3.7) vs. 3.1 (1.9-3.3) nmol/mg protein) compared to placebo. Between butyrate and placebo no statistical differences were found in TEAC (136.2 (116.2-207.6) vs. 137.2 (112.6-210.7) nmol trolox Eq/mg protein), GST (0.3 (0.4-0.4) vs. 0.3 (0.2-0.5) U/mg protein), GSSG (0.3 (0.1-2.7) vs. 0.4 (0.2-2.1) nmol/mg protein), MDA (0.8 (0.4-1.4) vs. 1.1 (0.7-2.2) nmol/mg protein) and GSH/GSSG ratio (54.5 (9.5-156.2) vs. 40.8 (9.3-84.3)). In addition, a significant positive correlation was found between MDA and GSSG ($R^2=0.35$, $p<0.01$), and a significant negative correlation between MDA and the GSH/GSSG ratio ($R^2=0.27$, $p<0.01$).
Conclusion: Butyrate enhances the anti-oxidant defense capacity as indicated by the increase in the amount of GSH. Also a decrease UA was found, which might be due to an inhibitory effect of butyrate on xanthine oxidase, the enzyme that catalyzes UA production. In addition, the correlations between the MDA and the GSH/GSSG ratio and GSSG support the validity of these assessments in colonic biopsy samples from healthy individuals.

**Enteral nutrition reduces the risk of mortality and infectious complications in patients with predicted severe acute pancreatitis: a meta-analysis comparing enteral and parenteral nutrition**

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The standard treatment for patients with acute pancreatitis is nil by mouth and intravenous administration of fluids. In patients with the mild form of the disease, a return to normal feeding is possible within several days. In severe acute pancreatitis nutritional support is an established treatment modality: not only to put a stop to further nutritional deterioration, but also to prevent secondary bacterial infection of (peri-)pancreatic necrosis. However, it is still unclear what the optimal method for nutritional support is: enteral nutrition (EN) or parenteral nutrition (PN). The objective of this study was to compare the effect of EN versus PN in patients with predicted severe acute pancreatitis in terms of clinically relevant outcomes. A computerized literature search was performed in the Medline, Embase and Cochrane databases. The search yielded 253 publications of which 30 would potentially meet the inclusion criteria: 1) the study design was a randomized controlled trial (RCT), 2) the study population was patients with predicted severe acute pancreatitis, 3) the intervention arms were EN and PN, 4) The outcome variables needed to include at least three of the following: total infectious complications, pancreatic infections, need for surgery, non-pancreatic infections, non-infectious complications, organ failure, length of hospital stay and in-hospital mortality. A total of 5 RCT fulfilled the inclusion criteria. Information on study design, patient characteristics, and acute pancreatitis outcomes were independently extracted by two authors using a standardized protocol. A meta-analysis of the 5 RCT's was carried out using a random-effects model. A total of 202 patients were included, of whom 95 received EN and 107 received PN. Enteral feeding reduced the risk of total infectious complications (relative risk [RR], 0.44; 95% confidence interval [CI], 0.29-0.67; p<0.001), pancreatic infections (RR, 0.48; 95% CI, 0.26-0.91; p=0.02), need for surgical intervention (RR, 0.37; 143 95% CI, 0.21-0.65; p=0.001) and mortality (RR, 0.31; 95% CI, 0.11-0.88; p=0.03). The risk reduction for organ failure did not reach statistical significance (RR, 0.76; 95% CI, 0.50-1.16; p=0.21).Conclusion: In patients with predicted severe acute pancreatitis, EN results in a clinical relevant and statistical significant risk reduction for total infectious complications, pancreatic infections and mortality.

**High-fat enteral nutrition reduces hepatic damage following combined exposure to bacterial DNA and hemorrhagic shock**

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Bacterial DNA is characterized by CpG motifs and has been shown to severely exacerbate the proinflammatory response following hemorrhagic shock via priming of inflammatory cells. Previously, we showed that high-fat nutrition strongly reduces the inflammatory response following hemorrhagic shock by stimulation of the autonomic nervous system via cholecystokinin. In this study, we investigated the effect of high fat nutrition on liver damage following combined exposure to oligodeoxynucleotides containing CpG motifs (CpG-ODN) and hemorrhagic shock. Rats were exposed to CpG-ODN or control ODN (nonCpG) before hemorrhagic shock (n=7 per group). Hemorrhagic shock was induced by withdrawing 2.1 ml blood/100 gram body weight. Subsequently, plasma and tissue samples were collected after 4 hours. The liver-specific, intracellular protein L-FABP was determined by ELISA. A marker for cell integrity (F-actin) was determined using immunofluorescence. Apoptosis was assessed by immunofluorescent staining of activated caspase-7.Combined exposure to CpG-ODN and hemorrhagic shock strongly enhanced circulating levels of L-FABP (1070±63 ng/ml, $P<0.01$), compared with rats exposed to nonCpG before hemorrhagic shock (L-FABP; 422±24 ng/ml). Furthermore, F-actin distribution in the liver was disturbed and there was an increased staining for activated caspase-7 in liver sections, indicating loss of cell integrity by apoptosis. Enteral administration of high fat nutrition to rats subjected to combined exposure to CpG-ODN and shock, strongly reduced circulating levels of L-FABP (437±22 ng/ml, $P<0.01$) and diminished disruption of F-actin distribution in the liver. Apoptosis was also strongly reduced as evidenced by staining for activated caspase-7.In conclusion, this study shows for the first time that enteral administration of high-fat nutrition prevents hepatic damage caused by exposure to bacterial DNA and ischemia. Inhibition of the inflammatory response and thereby reduction of apoptosis of liver cells by nutritional stimulation of the autonomic nervous system via high fat, seems a likely underlying mechanism.

**Formula feeding leads to decreased gut barrier function and an excessive systemic inflammatory response to luminal bacterial endotoxin**

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Necrotising enterocolitis is a devastating inflammatory disease, mostly affecting the ileum of premature infants. Formula feeding is an important risk factor for the development of this condition with a high morbidity and mortality. In this study we investigated the influence of formula feeding on gut barrier function and the systemic inflammatory response to enterally administered bacterial endotoxin (lipopolysaccharide, LPS). Sixty Sprague Dawley rats were divided equally at birth into either dam or formula fed groups. On day four 20 rats from each group were challenged with an intragastric bolus of LPS (1 mg / 10 g body weight). Control rats (10/group) received identical volumes of saline. The animals were sacrificed after two or four hours. Western blotting of intestinal tight junction proteins ZO-1 and Claudin-3 was performed, and semi-quantitatively analyzed using Quantity One (Biorad). Systemic cytokine levels were measured using Bio-Plex Protein Array System and a rat Cytokine 9-plex Panel (Biorad, Hercules, CA). The ileum of formula fed animals showed significantly less ZO-1 and Claudin-3 compared to dam fed littermates. Luminal exposure to LPS resulted in significantly decreased ileal concentrations of ZO-1 and Claudin-3 in both groups. In parallel the LPS challenge led to an evident pro- and anti-inflammatory response, with significantly enhanced plasma levels of TNF-$\alpha$, IL-1$\alpha$, IL-1$\beta$ and IL-10. However, formula fed rats showed significantly higher cytokine levels than dam fed controls.In conclusion formula feeding resulted in evidence of impaired gut barrier function in neonatal rats. We suggest that this impaired barrier function is involved in the enhanced inflammatory response to luminal bacterial endotoxin. These data offer new approaches for the search for the etiology of NEC.

**Comparison of ileal and duodenal brake mechanisms on satiety and gastrointestinal transport.**

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In both the duodenum and ileum, exposure of the luminal wall to nutrients activates a negative feedback mechanism. This duodenal and ileal brake are known to reduce food intake and hunger, and to inhibit gastric emptying and small bowel transit. In order to compare the ileal and the duodenal brake mechanisms, we performed a single-blind crossover study to compare the effects of fat emulsions infused either in the ileum or in the duodenum on satiety, food intake and gastrointestinal motor transport. Fifteen healthy female normal weight volunteers (mean age 23yrs, mean BMI 22 kg/m2) were intubated with a 270-cm naso-ileal tube, and participated in two experiments performed in random order on two consecutive days. Each test day after consumption of a fat-free liquid meal (180 kcal) at t=0 min, a emulsion consisting of 6g fat was administrated either into the duodenum or into the ileum from t=30-90 min after meal ingestion. Satiety parameters (visual analogue scales), blood samples (plasma CCK, PYY), gastric emptying with 13C-acetate breath test and small bowel transit time (SBTT) with lactulose H2 breath test were assessed at regular intervals. Food intake was assessed during an ad-libitum meal at t=240 min.Ileal fat induced a significantly stronger inhibition in appetite and hunger compared to duodenal fat (Appetite: 41.6 vs 49.9 mm/min, SE=2.0, p=0.004, Hunger: 39.0 vs 44.0 mm/min, SE=2.1, p=0.08). However, no significant differences were foud between ileal and duodenal fat with respect to food intake. Ileal infusion of fat caused a significant delay in gastric emptying (206 vs 138 min, SE=10.3, $p<0.05$) and in small bowel transit time (ileum vs duodenum 144 vs 85 min, SE= 13.7, p=0.005) compared to duodenal fat.No significant differences were seen in CCK and in PYY-secretion (CCK AUC 0.56 vs 0.51 pM/min, SE= 0.05, PYY AUC: 22.7 vs 25.4 pM/min, SE=1.04) between the duodenal and ileal infusion. However, the pattern of CCK- and PYY-secretion was different with significantly higher levels in the early phase of the test day in response to duodenal fat, and significant higher levels in the late phase in response to ileal fat.Conclusions:Ileal fat more potently inhibits hunger, gastric emptying and small bowel transit compared to duodenal fat. Thus, the ileal brake appears to be more potent compared to the duodenal brake.

**Evidence for modulation of leukocyte count but not neutrophil activation in healthy humans after intravenous administration of long- and medium-chain-based parenteral lipid emulsions**

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The use of total parenteral nutrition (TPN) confers an increased risk for infectious complications in which immune modulation by parenteral lipids seems to play a role. We previously have shown that emulsions containing mixed long- and medium-chain triglycerides (LCT/MCT) or pure medium-chain triglycerides (MCT), but not pure long-chain triglycerides (LCT), impair crucial neutrophil functions, alter calcium-mediated cell signaling kinetics and membrane fluidity and induce neutrophil activation in vitro.The present study was conducted to test the hypothesis that the mentioned lipids also distinctly modulate immune functions in the in vivo setting, in healthy humans. Therefore, we administered saline, LCT or LCT/MCT intravenously for 3.5 hours to healthy subjects (n=12) in a randomized cross-over design with a wash-out interval of two weeks. During this infusion, triglyceride concentrations were clamped at a clinically relevant level (3-5 mM). Leucocyte population counts and neutrophil activation, including stimulus-induced oxygen radical production and intracellular calcium signaling as well as the expression of relevant adhesion and degranulation markers (CD11b, CD66b, CD63 and CD62L), were determined pre- and post-infusion. While LCT exerted no effect whatsoever compared to saline, LCT/MCT infusion decreased lymphocyte counts by 44% (p=0.004, compared to saline and LCT). All infusions, including saline, increased absolute neutrophil count. This increase tended to be highest after exposure to LCT/MCT (130%) compared to saline (54%, p=0.10) and LCT (61%, p=0.12). Monocyte numbers were not affected by either treatment. In contrast to our in vitro results, neither lipid emulsion induced relevant signs of neutrophil activation or modulated the stimulus induced intracellular calcium signaling in neutrophils. Conclusions: in vivo exposure of humans to LCT/MCT, but not LCT, modulates leukocyte population counts, but, in clear contrast to in vitro exposure, does not induce neutrophil activation.

## A critical appraisal of clinical practices regarding endoscopically placed naso-jejunal-feeding tubes: a prospective single-center study

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Postpyloric feeding is indicated whenever patients cannot meet their nutritional needs due to a passage problem at the gastric level. Although guidelines are available on how to overcome this situation it remains unclear whether these are applied in clinical pracice. This notion initiated the present observational study where we evaluated clinical practices regarding endoscopically placed nasojejunal-feeding tubes (ENFTs). During a four-month observation period, 131 consecutive patients who were referred for ENFT placement were enrolled. ENFT placement was performed under direct vision using a Ch.10 polyurethane tube. Criteria for ENFT placement comprised severe gastro-oesophageal reflux, gastroparesis leading to aspiration, or delayed gastric emptying (residues two times > 100 ml within four hours not responding to prokinetics). The study endpoint was met in case the ENFT was no longer needed or the patient was discharged.During the observation period, 131 patients (84 males, mean age 59 yrs (17-87), of which 57% ICU patients; mostly with gastroenterological (41%) or cardiac (24%) problems) were enrolled. In only 59% of all patients ENFT placement met one of the mentioned criteria, while in ICU patients an even lower proportion (50%, p=0.01) was noted. In the latter group, in 35% of all cases no increased gastric residues had actually been measured. Of all ENFTs, 34 dislocated (26%), of which 21 (16%) within one week. Of all requests, 51% were completed within one day, and 79% within 48 hours. Especially with ICU requests, withdrawals (27%) were frequent, mostly as a consequence of recovered gastric emptying. No procedural complications were observed, only one significant accidental finding was reported (duodenal adenoma). Small gastric mucosal erosions, most likely caused by gastric feeding tubes were seen on a regular basis, but none provoked significant bleeding or required intervention.From these data we conclude that, at least in our institution, the guidelines that are at hand for ENFT placement are frequently not followed in clinical practice. Evidently, this matter deserves more attention to prevent unnecessary strain on both our patients as well as hospitals' budget.

**Does the route of administration (enteral or parenteral) of isotopically labelled L-glutamine affect the conversion of L-[2-15N]glutamine into L-[2-15N]arginine in humans**

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Background and aims:L-glutamine and L-arginine exhibit numerous beneficial effects in experimental and clinical studies. A pathway of L-glutamine into L-citrulline and L-arginine, involving intestinal and renal site-specific enzymes, has been suggested in the literature. The present study was designed to establish the effect of the feeding route, enteral or intravenous, on the conversion of L-glutamine into L-arginine at organ level in humans.Methods:Sixteen patients undergoing upper gastrointestinal surgery received an intravenous or enteral infusion of L-[2-15N]glutamine (15.7 ± 0.7 µmol/kg/hr). Blood was sampled from a radial artery and from the portal and right renal vein. Amino acid concentrations and enrichments were measured and net fluxes of 15N labelled substrates across the portal drained viscera (PDV) and kidneys were calculated (([A]-[V])* plasma flow). Results are expressed in mean ± SEM. Differences between the intravenous (IV) and enteral group (EN) were tested using Student's t-test. A p-value <0.05 was considered to indicate statistical significance.Results:Arterial L-[2-15N]glutamine enrichments were significantly lower during enteral tracer infusion (cTTR% IV: 6.66 ± 0.35 vs. EN: 3.04 ± 0.45; p<0.01), reflecting first pass intestinal metabolism of L-glutamine during absorption. Compared with intravenous administration, enteral administration of L-[2-15N]glutamine resulted in a significantly higher intestinal fractional extraction of L-[2-15N]glutamine (IV: 0.04 ± 0.07 vs. EN: 0.31 ± 0.11 µmol/kg/hr; p=0.02). Furthermore, enteral administration of L-[2-15N]glutamine resulted in higher arterial enrichments of L-[2-15N]citrulline (cTTR% IV: 5.52 ± 0.44 vs. EN: 8.8 ± 1.1; p=0.02), and both routes of administration generated a significant enrichment (p<0.01) of L-[2-15N]arginine. This was accompanied by intestinal release of L-[2-15N]citrulline across the PDV, which was highest with enteral administration of L-[2-15N]glutamine (IV:-0.36 ± 0.07 vs. EN:-0.68 ± 0.11 µmol/kg/hr; p=0.03), and renal L-[2-15N]arginine release in both groups.Conclusion:The gut prefers the uptake of enteral administered L-glutamine to intravenously provided L-glutamine, independent of the L-glutamine supply. Also, the route of administration, enteral or intravenous, affects the quantitative conversion of L-glutamine into L-citrulline, which is a precursor for renal L-arginine synthesis in humans.

## Faecal weight to diagnose malabsorption at the Intensive Care Unit

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Nutrition support is pivotal in the treatment of intensive care (ICU) patients. Diarrhoea occurs frequently in enterally fed ICU-patients. Recently, we have demonstrated that malabsorption is a commonly occurring and so far under diagnosed problem, strongly contributing to a negative energy balance in one of three of ICU patients with loose stools. The purpose of this prospective and controlled study was to evaluate faecal weight as a diagnostic tool to distinguish between patients with and without malabsorption. The energetic value of 3 days collected faeces was determined by bomb calorimetry. The total amount of enteral nutrition provided, which was calculated to be the necessary and adequate enteral intake for the particular patient by means of energy expenditure (established once during study period by indirect calorimetry). Absorption capacity was defined as: total amount of energy enterally provided minus the fraction of energy found in the faecal material divided by the amount of energy that was enterally provided x 100%. Malabsorption was defined as an energetic absorption capacity of 85% or less, according to Southgate (Br J Nutr 1970; 24(2):517-535). Patients were classified as having loose stools (group 1) with >250 gram faeces per day and classified as having normal stool-production (group 2) if the faecal weight was <250 gram per day. A total of 27 stable, fully enterally fed ICU patients were supplied with a faeces collector and completed the study (13 female, 14 male), aged 33-90 years. Patients in group 1 (n=10) were comparable to patients in group 2 (n=17) for sex, age, length, weight, energy intake and APACHE II. The mean (± SD) faeces production was 156 (± 67) and 742 (± 965) gram per day, mean faecal energy loss was 125 and 436 kcal/d, and subsequent energy absorption capacity was 94 (± 5%) and 78 (± 15%) in group 1 and 2, respectively. There was a statistically significant correlation (Fischer exact, p=0.01) between less or more than 250 gram faeces per day and energy absorption capacity (Cramers's V 0.71, p=0.01). Sensitivity and specificity amounted 94% and 78%, positive and negative predictive value were both 88%. In conclusion, a daily amount of faeces of 250 grams or more was a helpful clinical biomarker of intestinal malabsorption in ICU patients with a sensitivity and PPV approximating 90%). Recalculation and adaptation of nutritional needs are warranted in these patients.

## Development of a nomogram to predict complications after esophagectomy for cancer

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Introduction: Current predictive models in esophageal surgery mainly focus on predicting mortality but this is difficult, because it is a relatively rare event. However, esophagectomy is associated with a high incidence of complication related morbidity. A model which focuses on the severity of complications might be wider applicable. The aim of this study was to define a nomogram with use of conventional and widely available preoperative risk factors to predict the severity of complications in patients who underwent potentially curative esophagectomy. Methods: A consecutive series of patients who underwent potentially curative esophagectomy for cancer of the esophagus between January 1993 and August 2005 were used to construct a prognostic model. Complications were categorized according to the therapeutic consequences of these complications. Ordinal logistic regression analysis was performed to predict the grade of complications which were merged into four categories; No complications, mild complications (grade I and II), complications which need an (surgical or radiological) intervention (grade IIIa and IIIB) and severe complications (grade IVa, IVb and death). Results: A total of underwent esophagectomy. 197 patients (30%) had no complications, 246 patients (37%) had mild complications, 108 patients (16%) needed a reintervention and 112 patients (17%) experienced severe complications. The O-POSSUM and ASA classification did not have a relation with the severity of complications (p=0.126 and p=0.71 respectively). The present model was derived after backward elimination. This reduced model contained the following six variables; Age, q-waves or ST-T changes in the electrocardiogram, forced expiratory volume (FEV1), cerebrovascular accident or myocardial infarction in the medical history and operation type. A nomogram of this reduced model was constructed. This simple tool enables risk prediction for individual patients. The model showed adequate agreement between observed and predicted outcome probabilities in a prospectively collected cohort of patients operated upon between Aug. 1 2005 and Aug. 1 2006.Conclusions: A nomogram was developed to predict the severity of complications in individual patients who underwent potentially curative esophagectomy for cancer. The model may be used in everyday practice for preoperative counselling of patients and may have a role risk-adjusted audit of morbidity after esophagectomy.

**Nurse-led follow-up of patients after esophageal cancer surgery: a randomized trial**
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A surgical resection for esophageal cancer is accompanied by significant morbidity and impact on quality of life of patients. It is important that in this group of patients disease-related symptoms and patient's questions regarding prognosis should be adequately addressed during follow-up visits. The aim of this study was to compare home visits by a specialist nurse with routine control visits to the outpatient clinic with regard to quality of life, patient satisfaction and cost-effectiveness of follow-up after intentionally curative surgery for esophageal cancer.Between January 2004 and February 2006, 109 patients were randomized to standard follow-up by surgeons at the outpatient clinic (usual care; n=55) or by regular home visits by a specialist nurse (nurse-led follow-up; n=54) at 6 weeks and 3, 6, 9 and 12 months after surgery. Longitudinal data on generic (EORTC QLQ C30, EQ-5D, HADS) and disease specific quality of life (EORTC OES18), patient satisfaction and cost were collected at baseline at 6 weeks postoperatively and at 4, 7 and 13 months afterwards. Differences in outcome over time were assessed by analysis of variance, chi-square tests and Mann-Whitney tests.A significant and clinically relevant improvement in the eating scale (EORTC OES18), and in the fatigue, physical, role and social functioning scales and global health (EORTC QLQ C30) were found during follow-up in both groups, whereas other scales, for example pain and dysphagia (EORTC OES18) remained almost stable. We found no significant differences in quality of life scores between the two follow-up groups over time. In addition, no differences were found for patient satisfaction between the two groups. In total, 11 (20%) patients in the nurse-led follow-up group and 16 (29%) patients undergoing usual care developed metastases at a median of 8 months after randomization (p=0.29). Mean hospital stay was 3.6 days for nurse-led follow-up versus 7.0 days for usual care. Total medical costs, including follow-up, hospital stay, diagnostic procedures, retreatments and extramural health care, were significantly lower for nurse-led follow-up than for usual care (€ 1840 vs. € 2750; p=0.045).Conclusions: Patients after curative esophageal cancer surgery can safely be followed up by regular home visits of a specialist nurse. This alternative follow-up is less costly compared to usual care and does not adversely affect quality of life and patient satisfaction.

**Additional value of external ultrasonography of the neck after normal CT-scan in the preoperative assessment of patients with oesophageal cancer**

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In patients with oesophageal cancer extensive preoperative diagnostic work-up is essential to correctly identify potentially curable patients, preferably without the burden of too many investigations. Lymphatic dissemination of a (non-cervical) oesophageal tumour to the neck is considered as distant metastasis precluding potentially curative surgery. According to the 2006 CBO-guidelines multidetector computed tomography (CT) of the chest and abdomen is indicated to detect haematogenous dissemination. The standard CT-scan also includes the lower cervical region. Additionally, lymphatic dissemination to the lower neck can be assessed by external ultrasonography (US) in combination with fine needle aspiration (FNA). It is unclear whether external US (+FNA) should be applied in all patients or can be limited to patients with suspected cervical lymph nodes on CT in order to obtain cytological confirmation. Therefore, the aim of this study was to determine the additional value of external US to detect lymphatic metastasis to the neck after normal CT-scanning. Between January 2003 and December 2005, 307 patients were analysed in our department for oesophageal cancer. A total of 234 patients underwent both CT and external US of the neck. FNA was only performed if external US reported suspected lymph nodes. FNA was defined as gold standard. After extensive diagnostic work-up 141 of 234 patients (60%) were eligible for potentially curative oesophagectomy. The remaining 93 patients (40%) did not undergo surgery, mainly due to incurable disease. CT identified suspected nodes in 57 of 234 patients (24%), of whom 28 patients also had suspected nodes on external US. FNA confirmed metastasis in 10 of these 28 patients. In 177 patients (76%) CT did not identify any suspected nodes, but external US disagreed in 36 of them. In nine of these patients FNA confirmed metastasis, resulting in an additional value of external US after normal CT-scanning of 5% (9/177). This study shows that external US (+ FNA on indication) of the neck has an additional value of 5% in detecting lymph node metastasis in the lower cervical region after normal CT-scanning. Considering its non-invasiveness and wide availability in combination with the importance of the potential therapeutic consequences, external US of the neck should be part of the routine diagnostic work-up in patients with oesophageal cancer, even after normal CT-scanning.

## The role of Immunoglobulin M, C-reactive protein and complement in liver ischemia-reperfusion injury

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A role for C-reactive protein (CRP) and Immunoglobulin M (IgM) in the initiation of I/R injury via complement activation has been established in various I/R models. Both CRP and IgM can bind to neoantigens in the damaged cell membranes leading to the activation of complement. However, the time course in which IgM and CRP activate complement in liver I/R remains unknown. The aim of this study was to assess the relationship in time of IgM and CRP binding in comparison to complement activation in a hepatic I/R rat model. Male Wistar rats (n=60) were divided into eleven groups: 60 minutes of partial ischemia (70%) followed by 0, 3, 6, 12 or 24 hours of reperfusion (each n=6). Partial ischemia was induced via clamping of the left segmental portal triad. Sham laparotomy groups with corresponding reperfusion times were included, as well as a control group sacrificed before ischemia (each n=5). Hepatocellular injury (histopathology scored on a scale from 0-12 and plasma aminotransferases), inflammatory response (neutrophil influx), IgM content in ischemic hepatic tissue homogenates as determined by ELISA and immunohistochemical depositions of CRP, IgM and C3 on frozen tissue sections were assessed during each reperfusion time. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) significantly increased after 3 hours and remained elevated up to 24 hours, peaking at 6 hours (5300 ± 1000 and 3100 ± 800 U/L, respectively) ($p<0.05$ versus sham). Hepatic neutrophil influx was significantly increased from 3 to 6 hours of reperfusion ($p<0.05$), peaking at 12 hours (1.1 ± 0.2 U/mg protein) ($p<0.05$). Histopathological injury increased from 3 to 12 hours of reperfusion and remained elevated thereafter ($p<0.05$ versus sham). Rat IgM content in ischemic tissue homogenates demonstrated a progressive increase throughout reperfusion up to 24 hours ($p<0.05$ versus sham). Immunohistochemical analysis showed a similar staining pattern of IgM and C3 (Spearman rank-correlation test $r(S)= 0.79$, $p< 0.01$), in which depositions increased from 3 to 6 hours of reperfusion and significantly decreased at 24 hours. CRP depositions peaked at 3 hours of reperfusion and significantly decreased throughout reperfusion until 24 hours ($p<0.05$ versus 3 hours).These data suggest that both IgM and CRP are mediators of hepatic I/R-induced complement activation in rats, in which CRP-mediated activation appears to precede that of IgM.

**Anaesthesiological considerations on small-incision and laparoscopic cholecystectomy in symptomatic cholecystolithiasis: implications on pulmonary function in a randomized clinical trial**

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Upper abdominal surgery including laparoscopic cholecystectomy (LC) is associated with postoperative pulmonary dysfunction. LC has, by consensus, become the treatment of choice for symptomatic cholecystolithiasis. However, the small-incision cholecystectomy (SIC) is a valuable alternative which is technically safe and does not require a pneumoperitoneum. We hypothesize that the SIC technique might be superior to the LC when considering postoperative pulmonary function.A single-centre randomized clinical trial was performed including patients scheduled for elective cholecystectomy. Pulmonary flow-volume curves were measured preoperative, postoperative, and at follow-up. Blood gas analyses were measured preoperative, in the recovery phase and on postoperative day one. Surgical residents principally performed the operations. Anaesthesia and analgesics were standardized by protocol. Patients were randomised after induction of anaesthesia. Postoperatively, patients and caregivers were blinded to the procedure by applying identical wound dressings. A total of 257 patients were randomised (LC:120 and SIC:137). There was one pulmonary complication (pneumonia) in the LC group. Conversion rates were similar. In both groups a similar reduction in all pulmonary function parameters occurred, with complete recovery to preoperative values at six weeks postoperative. Patients converted to a conventional open cholecystectomy showed significant differences in six of the eight parameters in pulmonary function tests. Patients in the SIC group consumed more postoperative analgesia when compared to the LC group. Even with strict methodology and standardization of care (e.g. single-centre trial and protocols for premedication, anaesthesia and analgesics), no significant differences between SIC and LC regarding pulmonary function were found. Our results are generalisable to non-expert settings and raise the question of which arguments remain to support the popularity and assumed superiority of LC.

**Cost-minimisation analysis in a blind randomised trial on small-incision versus laparoscopic cholecystectomy from a societal perspective. Sick leave outweighs efforts in hospital savings.**

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Laparoscopic (LC) and small-incision cholecystectomy (SIC) are two alternative techniques for cholecystectomy. In a recent Cochrane review no differences have been found between both techniques considering complications, conversions, hospital stay and convalescence. A quicker operative time was found in SIC. In absence of clear clinical benefit it may be interesting to focus on the resource use. We performed a blinded randomised clinical trial focussing on a difference in costs between LC and SIC. The trial was performed from a societal perspective with emphasis on internal validity and generalisability in a general teaching hospital in the Netherlands. Patients with reasonnable to good health diagnosed with symptomatic cholecystolithiasis scheduled for cholecystectomy were included and patients were randomised between LC and SIC. In this cost-minimisation analysis, all resources of 257 randomised patients were prospectively recorded. All direct medical costs were summarised in different categories including costs due to complications. Tariffs, cost prices and budget prices were distinguished. It was estimated that 120 patients per group would be needed to detect a difference of 10% in direct costs.A total of 257 patients were randomised between LC (120) and SIC (137). There were no significant differences in complications, conversions, and hospital stay. Operative time was significantly shorter in SIC. Operation theatre costs were over 23% more expensive in the LC group compared to the SIC group (LC: 1112 euro compared to SIC: 901 euro; difference 211 euro, $p<0.001$). There were no significant differrences in the other direct cost categories (outpatient clinic and admittance related costs), indirect costs, and total costs. More than 60% of costs in employed patients are caused by sick leave.Small-incision cholecystectomy is the preferred operative technique over the laparoscopic technique from an operation theatre, hospital, and societal cost perspective. Sick leave associated with convalescence after surgery in employed patients results in considerable costs to society.

**Timing of cholecystectomy after endoscopic sphincterotomy for common bile duct stones.**

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The goal of this study was to determine whether in patients with combined cholecystocholedocholithiasis, the timing of laparoscopic cholecystectomy (LC) after endoscopic sphincterotomy (ES), does affect the outcome of LC. According to the literature, conversion rate of LC after ES is as high as 20%, at least when performed after 6-8 weeks. It is hypothesized that early planned LC after ES reduces recurrent biliary symptoms and conversion rate. All patients who underwent LC after ES between 2001 and 2004 were evaluated. Recurrent biliary symptoms during waiting time for LC, conversion rate, postoperative complications and hospital stay were documented. Data were analyzed using the Student's t-test. 167 consecutive patients (M:F=59:108, median age 54 years) were analyzed. The median interval between ES and LC was 7 weeks (IQR 2-13 weeks). During waiting time for LC, 33 patients (20%) had recurrent biliary complications. These consisted of cholecystitis (n=18, 11%), recurrent choledocholithiasis (n=9, 5%), cholangitis (n=4, 2%) and biliary pancreatitis (n=2, 1%). 15 of these patients underwent a second ERC. Median time between ES and development of recurrent complications was 22 days (IQR 8-47 days). 76% of the biliary complications occurred more than 1 week after ES. Conversion to open cholecystectomy occurred in 13% of all patients. However in patients with recurrent complications during the waiting period, conversion rate was 21% (versus 10% in uncomplicated patients; p=0.048). Also, there was significantly more morbidity when recurrent complications occurred during the waiting period (24 % versus 11%, p=0.026). This concurred with a significant longer hospital stay (median 4 versus 2 days, p<0.001).Conclusion. In this study, during the waiting period for cholecystectomy after ES, 20% of all patients had recurrent biliary complications. These recurrent complications are associated with second ERC, a higher conversion rate, more morbidity and a significantly longer hospital stay. Presumably, earlier surgery after ES can prevent these negative results. A prospective randomized clinical trial has been initiated.

## Postoperative enteral feeding after pancreatoduodenectomy

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Backround: Morbidity after pancreatoduodenectomy (PD) remains high: approximately 50 % of patients have postoperative (po) complications. In malnourished patients the administration of po enteral nutrition is known to reduce po morbidity. At our centre standard strategy was to administer enteral nutrition through feeding jejunostomy. This strategy was changed in 2000 to resection without feeding jejunostomy. In the present study we evaluated the effect of this change in strategy on po outcome.
Methods: From 1996 to 2004, 449 consecutive patients underwent PD. Before 2000 patients received a jejunal feeding tube as a standard procedure. After 2000 feeding strategy was changed. Only patients with severe malnutrition (> 10 % of total body weight weight loss) received a jejunal feeding tube. Data on number of days nasogastric intubation, delayed gastric emptying (DGE), po feeding, hospital stay and po morbidity and mortality were evaluated from our prospective database.
Results: 209 (46.5%) patients received a jejunal catheter during surgery (group A), 240 (53.5%) patients did not receive a jejunal catheter (group B). Number of days of nasogastric intubation was 4 days (median) for both groups. In group A 49 patients (23.4%) had DGE vs. 39 patients (16.3%) in group B ($p=0.06$). 41 patients (17.1%) in group B eventually had postoperative enteral nutrition through a jejunal tube. Total parenteral nutrition (TPN) was given to 14 patients (3.1%) in group A vs. 33 patients (7.4%) in group B ($p=0.03$). In group A po hospital stay was 15 days (median) vs. 13 days (median) for group B ($p<0.01$). Po morbidity was 49.8% in group A and 50.4% in group B (NS). 71 patients had infectious complications in group A (34.0%) and 91 patients in group B (37.9%; NS). Mortality was not different (1.0% vs. 2.1%; group A and group B, respectively; NS).
Conclusions: Po enteral nutrition by a jejunal catheter did not influence number of days patients had nasogastric intubation, general complications or mortality. Since morbidity did not increase by omitting a jejunal feeding cathter after PD, this study supports our change in strategy. Patients after PD do not require standard po jejunal feeding catheter. Enteral feeding is however indicated in patients with DGE or prolonged po course.

**Extracapsular lymph node involvement in node positive patients with adenocarcinoma of the ampulla of Vater**

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The presence and extent of lymphatic dissemination is an important predictor of survival in patients with adenocarcinoma of the ampulla of Vater. Extracapsular lymph node involvement (LNI) and its impact on survival have been studied for several malignancies. No available literature to date describes the incidence of extracapsular LNI in adenocarcinoma of the ampulla of Vater and the clinical consequences.The aim of the present study was to assess the incidence and extent of extracapsular LNI in a consecutive series of patients with adenocarcinoma of the ampulla of Vater, that underwent a resection with curative intent. The relation with tumour stage and number of positive nodes was evaluated and the prognostic significance with respect to survival (tumour recurrence) was analyzed.Between Jan-1992 and Feb-2006, a consecutive series of 649 patients underwent pancreatoduodenectomy (PD) for a suspected periampullary malignancy. The clinicopathological data were prospectively collected. Hundred and sixty patients had an adenocarcinoma of the ampulla of Vater, positive lymph nodes were found in 75 patients (47%). Positive nodes were re-examined by a pathologist, experienced in the field of gastrointestinal malignancies. Follow-up data was collected at the outpatient clinic or by contacting general practitioners.For a total of 750 positive nodes, extracapsular LNI was identified in 100 (13% of the positive nodes), occurring in 44 of 75 lymph node positive patients (59%). The median potential follow-up period was 84 months (range 168). Overall median survival was 39 months (95% CI: 27-51 months) and 5-year actuarial survival was 37%. The median survival in patients without LNI (N0) was 104 months (95% CI: 61-146). The median survival in patients with only intracapsular LNI was 30 months (95% CI: 20-40) in comparison to 18 months (95% CI: 13-23) for those who had extracapsular LNI ($p<0.016$). Five-year survival rates were for N0, intracapsular LNI and extracapsular LNI, respectively 59%, 20% and 9%. Multivariate analysis demonstrated that for patients with positive lymph nodes, extracapsular LNI and tumor differentiation were independent prognostic factors for survival.The presence of extracapsular LNI identifies, in patients with an adenocarcinoma of the ampulla of Vater, a subgroup with a significantly worse long-term survival. Adjuvant therapy after resection, i.e. chemo- and/or radiation therapy, might be considered for this particular subgroup

## Indication, utilization, and yield of early CT scan in the management of acute pancreatitis

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Background: In 2003 a cohort study of acute pancreatitis (AP) in the province of Northern Holland (2,6 million inhabitants) was initiated (EARL study). One of its aims is to analyze the clinical management of AP in a population based setting, including the use of CT scan. Many patients do not require a CT scan at admission or during hospitalization. An early CT scan (within 96 hours after symptom onset) may be indicated to distinguish AP from other serious intra-abdominal conditions or to identify early pancreatic necrosis in patients with fever and septic signs or/and emerging organ failure to start prophylactic antibiotics.Methods: Patients were included from 18 hospitals. The following data were retrieved from the study database: etiological factors, hospitalization time, timing (after the onset of symptoms) of CT scan, Baltazar CT severity index, presence of pancreatic necrosis, and use and timing of antibiotics.Results: For this survey 141 admissions of 128 patients were analyzed. The etiology of AP was biliary (34,4%); alcoholic (15,6%); post-ERCP (14,1%); idiopathic (14,1%) and miscellaneous (21,8%). The median hospital stay was 8 days (1-52). At least one CT scan (range 1-6) was performed in 43,3% (61/141) of admissions and in 63,9% (40/61) the CT was made within 96 hours after symptom onset: 22,5% at admission, 10% after 24 h, 17,5% after 48 h, 22,5% after 72 h and 22,7% after 96 h. In 7,5% (3/40) there were differential diagnostic considerations to perform an CT. In 27,5% (11/40) the indication was persisting fever or a rising CRP. Only one patient (2,5%) showed evidence of sepsis at the time of CT. Importantly, in the remaining 62,5% (25/40) there were no clinical signs of necrosis/sepsis at the time of early CT. The Baltazar CT severity index was grade A (normal) in 17,5%; grade B in 22,5%; grade C in 45% and grade D in 15%. None of the early CT scans showed pancreatic necrosis. In a minority of 10% (4/40), early CT findings prompted the physician to start antibiotics. In 17,5% (7/40) (prophylactic) antibiotics had already been started before obtaining the CT.Conclusions: An early CT scan is frequently acquired in the early course of AP. Many early CT scans are performed at times when there is no true clinical suspicion of necrosis. Therefore, the yield is low with little clinical management consequences. Based on the outcome of this survey it seems prudent that clinicians should be more restrictive in the use

**Premature closure of the Dutch Stent-in I trial: Colonic stenting vs. surgery in left-sided colonic obstruction for incurable colorectal cancer.**

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The introduction of self-expandable metal stents (SEMS) has offered a promising non-surgical alternative for patients with incurable left-sided obstructive colonic cancer. The objective of this study was to compare palliative colonic stenting with surgery in terms of hospital free survival, quality of life, morbidity and costs. Patients with incurable left-sided colonic cancer were eligible for this randomized trial. Exclusion criteria were ileus, a Karnofsky score of less than 50 % or an ASA classification of IV or V. Patients' data and monthly follow-up on severity of obstruction, adverse events, general condition and quality of life questionnaires were prospectively collected. A high number of serious adverse events in the non-surgical group urged the Medical Ethical Committee to advise discontinuation of the trial prematurely. At that moment 21 patients had been randomized. Ten patients were randomized for surgery, 9 were treated accordingly, 1 patient died prior to surgery. Eleven patients were randomized for non-surgical palliation, in total 10 patients were treated with an enteral stent (WallFlex™, Boston Scientific, Natick, MA), one patient did not develop obstructive symptoms and was therefore not stented. Baseline demographics and clinical characteristics were similar for both groups. At a median follow-up of 289 days five patients were alive, 3 of the surgical and 2 of the non-surgical group. Of the 10 patients treated with an enteral stent 8 suffered one or more stent-related complications compared to 1 patient from the group of 9 who underwent surgical palliation (p= 0.005). Among the stent-related complications were 6 perforations, respectively 12, 12, 44, 106, 351 and 355 days after stent placement. A high rate of late stent-related perforations caused early closure of this study. Perforations were related to the design of the stent as well as to having the stented tumor in situ. Since this observation of late perforations has not been reported before, it is of paramount importance that patients being or having been treated with a colonic stent, in particularly the WallFlex™, will be prospectively followed in a registry.

## The prognostic significance of extracapsular lymph node involvement in node positive patients with colonic cancer

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Extracapsular lymph node involvement (LNI) is the extension of cancer cells through the nodal capsule into the perinodal fatty tissue. In colonic cancer little attention has been paid to the biological significance of extracapsular lymph node LNI. Aim of this study was to assess the incidence and prognostic significance of extracapsular LNI in colonic cancer.

Between January 1994 and May 2005, all patients who underwent segmental colonic resection for primary colonic cancer with lymph node metastasis were reviewed. All resected lymph nodes were reexamined to assess extracapsular LNI. In a uni- and multivariate analysis disease free survival was correlated with various clinicopathologic factors. Among these factors age, tumor diameter, total number of resected lymph nodes (i.e. tumor positive and negative) and lymph node ratio were dichotomized as less or more than the corresponding median value.

One hundred eleven patients were included in whom a total of 332 positive nodes were identified. Extracapsular LNI was found in 101 (30%) lymph nodes and in 58 (52%) patients. Univariate analysis revealed that pN-stage (5-year disease free survival pN1 vs. pN2; 65% vs. 14%, $p<0.001$), extracapsular LNI (5-year disease free survival intracapsular LNI vs. extracapsular LNI; 69% vs. 41%, $p=0.003$), and lymph node ratio (5-year disease free survival $< 0.18$ vs. $\geq 0.18$; 67% vs. 42%, $p=0.023$) were all significant prognostic indicators for disease free survival. Multivariate analysis demonstrated that among these variables pN-stage (hazard ratio 3.5, 95% CI: 1.72 – 7.42) and extracapsular LNI (hazard ratio 1.98, 95% CI: 1.00 – 3.91) were independent prognostic factors.

Patients without extracapsular LNI receiving adjuvant chemotherapy had a significantly better survival compared to patients who did not receive adjuvant chemotherapy ($p=0.010$). However, chemotherapy did not improve disease free survival in patients with extracapsular LNI.

Conclusion: The presence of extracapsular LNI identifies a subgroup of patients with a significantly worse long-term survival. Detection of extracapsular LNI in the surgical resection specimen might be helpful in the future to individualize postoperative therapeutic strategies in the adjuvant setting. Together with pN2 stage, extracapsular LNI reflects a particularly aggressive biologic behavior and has significant prognostic potential.

**Mucosal delivery of recombinant Hedgehog protein reduces the incidence of intestinal polyp formation**

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Hedgehog signaling is implicated in growth of esophageal, gastric, biliary, and pancreatic cancers but not in intestinal cancers**.** We set out to study the role of Hedgehog in carcinogenesis of the intestine.
We have engineered the food-grade bacterium *Lactococcus Lactis* to secrete bioactive murine Sonic Hedgehog (Shh). *In vitro* recombinant Shh production by *L. Lactis* and bioactivity of Shh was evaluated by Western blot, enzyme linked immunosorbent assay (ELISA), Gli-luciferase reporter and Alkaline Phosphatase assay. Wild type mice were used to measure the delivery of Shh protein by *L. Lactis* in the gastrointestinal tract and to study the effect of Shh on its target genes. $Apc^{+/min}$ mouse model of intestinal carcinogenesis was used to test the effect of recombinant Shh on the development of polyps in the intestine. During six weeks two groups of eight $Apc^{+/min}$ mice received daily inoculates of *L. Lactis* secreting Shh or empty vector carrying control *L. Lactis per gavage.*
Biological activity of *L. Lactis* derived Shh was confirmed *in vitro* in two cell-based assays of Hedgehog activity and *in vivo* the concentration of Shh in the murine jejunum and ileum was increased. Furthermore, induction of Shh-target Bmp4 was found in the mesenchyme of the intestine and this had a reciprocal effect on the phosphorylation of BMP signaling component Smad1 and BMP target gene Id2 in the intestinal epithelium. Treatment with LL-mShh reduced the incidence of polyp formation 61% in the ileum of $Apc^{+/min}$ mice (table 1).
Conclusion: Here we report that recombinant Hedgehog protein can be delivered locally to the intestinal mucosa using *L. Lactis*. Increased Hedgehog signaling induces reciprocal epithelial-mesenchymal signalling. Moreover, Hedgehog reduces the incidence of polyp formation in a mouse model of intestinal carcinogenesis showing that Hedgehog acts as a tumor suppressor in the intestine. Our data suggest that analogous approaches may constitute a novel strategy to reduce the rate of polyp formation in patients at high risk for the development of intestinal cancer.

**Adequately dosed 6-TG use in chronic intestinal inflammation is not associated with nodular regenerative hyperplasia: a series of 73 liver biopsies**

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BackgroundThe use of 6-thioguanine (6-TG) has been proposed as a rescue drug in patients with chronic inflammatory intestinal conditions, such as inflammatory bowel disease (IBD) and celiac disease, failing to tolerate or refractory to standard thiopurines. However, the use of 6-TG in IBD patients has been discarded due to previous reported hepatotoxicity, in particular nodular regenerative hyperplasia (NRH), associated with high dose 6-TG. Pathohistological data of 73 liver biopsy specimens acquired from patients using long-term and adequately (low-)dosed 6-TG are presented here.Methods:All liver biopsy specimens from patients with chronic inflammatory intestinal diseases treated with 6-TG for three months or longer in five hospitals in the Netherlands were examined. The specimens were classified by experienced liver pathologists and subdivided into 1. normal histology, 2. NRH, inconclusive pathohistological changes potentially NRH-related or aspecific regeneration, 3. sinusoidal dilatation or veno-occlusive disease (VOD), 4. PSC, or 5. fibrosis.Results:73 liver biopsy specimens were analyzed; 68 (93.2%) and 5 (6.8%) biopsy specimens were from patients with IBD and celiac disease, respectively. Of these specimens, 46.6% were acquired from male patients with a median age of 49.5 years (range 28-72 years); female patients had a median age of 41.0 years (range 22-65 years) (P= 0.026, Mann-Whitney test). The median 6-TG dosage was 20 mg daily (range 18-24 mg). The median duration of 6-TG use was 2.8 yrs (range 4-57 months). Normal histology was seen in 47/73 liver biopsy specimens (64.4%). None of the patients had a definitive diagnosis of NRH. Potentially NRH-related findings, although inconclusive, were found in 3/73 (4.1%) liver specimens, whereas aspecific regeneration was observed in 9.6%. Characteristics of pathological sinusoidal structure was detected in eight slides (11.0%). No VOD was found. Three liver slides showed PSC or inconclusive PSC. Fibrosis, but no cirrhosis, was observed in six liver biopsy specimens (8.2%).Conclusion:Although previous reports suggested NRH to be a common finding in patients treated with 6-TG in high dosages, no NRH could be found in 73 liver biopsy specimens from patients with IBD or celiac disease with long-term and adequately (low-)dosed 6-TG therapy. Hepatotoxicity, particularly NRH, is a dose-dependent adverse event of thiopurine use, and is not associated with adequately dosed 6-TG.

**A Prospective Follow-up Study on 163 Patients with Budd-Chiari Syndrome: Results From The European Network for Vascular Disorders of the Liver (EN-Vie)**

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Budd-Chiari syndrome (BCS) represents a challenging disorder with potential dismal outcome. Our current understanding has been derived from retrospective series with limited sample-size, as rarity precluded prospective research in the past. Recently, a collaborative effort between reference centers from nine European countries led to this first prospective cohort study.From October 2003 to October 2005, incident cases of BCS were nationwide identified and enrolled by co-ordinating centers. Diagnostic criteria included unambiguous radiographic evidence for hepatic venous outflow obstruction. Excluded was obstruction due to tumorous, cardiac and toxic causes. Data were collected at diagnosis, predefined intervals and significant clinical events. Blood samples were obtained for centralised etiological work-up and radiological images collected for expert review. Patients were followed from diagnosis until death, study closure (May 2006) or last visit.Out of 210 patients identified in 39 hospitals, 163 patients (93 females) were eligible for analysis. Median age was 38 years (16-83). Median follow-up was 17 months (range 0.1-31). According to the Rotterdam BCS index, expected 1-year survival was 82%. Radiology showed pure hepatic block in 50%, IVC block in 2%, combined block in 47% and concomitant portal vein obstruction in 15%. Myeloproliferative disorders were found in 47% of bone-marrow biopsies. V617F-JAK2 mutation, tested in all DNA samples, was detected in 29%. FV Leiden, FII gene and MTHFR mutations were present in 14%, 4% and 52%. Patients were treated with anticoagulation (n=141, 87%), TIPS (n=64, 39%) and/or OLT (n=20, 12%). Only 3 patients were treated by surgical shunt and 7 by recanalisation procedures alone. Seventy-seven patients (47%) were managed non-invasively. Twenty-nine patients died (18%), and 6-, 12- and 24-month survival was 90% (95%CI 85-95), 87% (95% CI 82-93) and 80% (95% CI 72-87), respectively. Leading cause of death was liver failure (n=8). Post-transplant mortality was 10%.

In conclusion, this international prospective study shows that (1) JAK2 mutation accounts for only 29% of incident unselected cases of BCS; and (2) current management based on anticoagulation and TIPS, with transplantation as salvage treatment, results in survival rates similar to those previously reported in retrospective cohorts where more aggressive surgery was the mainstay of therapy.

**Prophylaxis of post-ERCP pancreatitis: a randomized, placebo controlled trial using intravenous infusion of semapimod, a mitogen activated protein kinases inhibitor**

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Background: Acute pancreatitis and hyperamylasemia are frequent complications of endoscopic retrograde cholangiopancreatography (ERCP). Semapimod is a synthetic guanylhydrazone that inhibits the mitogen-activated protein kinase (MAPK) pathway, macrophage activation and the production of several inflammatory cytokines. This study evaluated whether intravenous administration of semapimod given before therapeutic ERCP reduces the incidence post ERCP hyperamylasemia and pancreatitis. Methods: In a single center (tertiary referral center and teaching hospital for advanced interventional endoscopy), randomised, double blinded trial, a single iv infusion of 50 milligrams semapimod given one hour before ERCP was compared with placebo in patients who required endoscopic sphincterotomy, stenting or other therapeutic procedures. The primary endpoint was the incidence of post-ERCP clinical pancreatitis, and a secondary endpoint was the incidence of hyperamylasemia. Post ERCP pancreatitis was defined by a more than threefold increase above the upper limit of normal in plasma amylase (>660 U/ml) or lipase (>180 U/ml), combined with an increase in VAS abdominal pain score relative to pre ERCP of at least 30 points (on a 1-100 scale) lasting for at least 24 hours.Results: A total of 242 patients were analyzed. The semapimod group (n = 121) and the placebo group (n = 121) were comparable for age, sex, indications for treatment, and types of procedure. No difference in serious adverse events was shown between patients treated with semapimod or placebo. The incidence of hyperamylasemia was significantly reduced (29.8% v 18.4%; p = 0.031). Moreover, semapimod administration significantly lowered the levels of amylase during the first 48 hours post ERCP. The incidence of clinical pancreatitis showed a trend towards a reduction (40%), but this did not reach statistical significance (14.9 vs 9.1%; p = 0.117).Conclusions: A single dose of 50 milligrams of intravenous semapimod one hour pre ERCP is safe and exerts a biological effect demonstrated by a statistically significant reduction of the incidence of hyperamylasemia and levels of post ERCP amylase, and a non-significant trend towards a protective effect for the development of post ERCP pancreatitis.

**Nurse endoscopy: preliminary evaluation of a colonoscopy training program**

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Background: Screening by colonoscopy is recommended in many countries to reduce the risk of death from colorectal cancer. Given the limited supply of medical endoscopists, nurse endoscopists may represent an economic alternative. Several studies are available that show that non-medical endoscopists can be trained to perform flexible sigmoidoscopy as safely and effectively as medical endoscopists. There are no such data on colonoscopy. We evaluated the performance and safety of our colonoscopy training program for nurse endoscopists in comparison with trainee medical endoscopists. Methods: Two gastrointestinal endoscopy nurses were enrolled in a colonoscopy training program, including theoretical sessions and computer-based colonoscopy simulation. Their first 100 colonoscopies in clinical practice under direct supervision were evaluated and compared with results from a medical trainee during the same time period. Only diagnostic procedures in patients with their entire colon in situ were included. Objective criteria for competency were cecal intubation rate, cecal intubation time, need for assistance and complications. Subjective criteria including pain and discomfort scores were assessed using a 10 point visual analogue scale (VAS; 0, none; 10 unbearable). Results: The overall unassisted nurse-performed cecal intubation rate was 83 %. The median cecal intubation time for the initial 25 procedures was 14 minutes (range 6-29), improving to 11 minutes (range 4-26) for the last 25 procedures. Median patients' pain and discomfort scores gradually decreased in the course of training from 3.1 to 2.0 and 1.7 to 0.2, respectively. Pathologic findings were detected in 51 % of procedures, which in all cases were recognized by the nurse endoscopists. No complications were observed. Cecal intubation rates and times and patient satisfaction, pain and discomfort scores were similar between nurse endoscopists and the medical trainee.
Conclusions: Endoscopy nurses can be trained to perform colonoscopy in a safe and effective manner, with results similar to those for trainee medical endoscopists.

**Screening and surveillance for colorectal carcinoma in patients with ulcerative colitis and Crohn's disease: Are current surveillance guidelines adequate? Interim analysis of a retrospective multi-centre descriptive study**

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Patients suffering from inflammatory bowel disease (IBD) have a higher risk of developing colorectal cancer (CRC) than the general population. In an attempt to detect precancerous dysplasia or asymptomatic cancer many of these patients enter a surveillance programme following American Gastroenterology Association (AGA) or British Society of Gastroenterology (BSG) guidelines. Based on disease duration and extent of disease these guidelines recommend initiating surveillance after 8-10 years of disease for Crohn's disease and extensive colitis, and after 15-20 years for left-sided colitis. Strong scientific evidence is not yet available for these starting points.
Furthermore, we encountered a number of IBD patients who developed CRC earlier than aforementioned starting points. Our aim was to assess the time-intervals between onset of IBD symptoms or diagnosis of IBD and diagnosis of CRC, and subsequently evaluate how many patients developed CRC before their surveillance is recommended to commence. We used a nationwide automated pathology database (PALGA) to identify patients with IBD-associated CRC in all university medical centres in the Netherlands. Only patients who had IBD and CRC diagnosed synchronously or metachronously in a pathology report from January 1990 until June 2006 were included.Thus far we collected data in 5 of 8 university medical centres on 104 patients with confirmed diagnoses of IBD and CRC, (male/female 65/39). Ulcerative colitis was diagnosed in 64 cases and Crohn's disease in 40. Median ages at IBD and CRC diagnoses were 29 years [6-83] and 48 years [21-85] respectively. Using date of diagnosis as entry-point and following the generally accepted guidelines, 26% of patients developed cancer before the start of surveillance. This even increased to 33% of patients if surveillance would commence at 10 or 20 years after diagnosis for extensive or left-sided disease respectively. Using onset of symptoms to calculate the time between IBD-diagnosis and CRC, a total of 18% of patients presented with cancer before 8 or 15 years of disease duration and 26% of patients before 10 or 20 years of disease duration, thus before the start of surveillance. In conclusion, these results suggest that the diagnosis of CRC might be delayed or missed in a substantial number of IBD patients (18-33%) when conducting surveillance strictly according to formal AGA and BSG guidelines.

**Endoscopic TriModality Imaging (ETMI) for the detection and classification of colonic polyps**

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Endoscopic detection and removal of colonic adenomas prevents the development of colorectal cancer. During standard colonoscopy 13-26% of small adenomas are missed and 17-40% of detected polyps are non-adenomatous. A new endoscopic trimodality imaging (ETMI) system has been developed, incorporating high resolution white light endoscopy (WLE), autofluorescence imaging (AFI) and narrow band imaging (NBI). In this ongoing randomized cross-over study we are assessing the value of ETMI for the detection and classification of colonic polyps in patients at increased risk for adenomas.Consecutive patients scheduled for surveillance colonoscopy are invited for this study. Segmental colonoscopic examination is performed with both WLE and AFI, in a randomized order. The sensitivity of primary adenoma detection is calculated as the number of detected adenomas divided by the total number of adenomas detected by both techniques. The accuracy of the Kudo classification by NBI is subsequently determined for the prediction of histology, which is being used as the gold standard. Furthermore, the accuracy of the combination of NBI and AFI will be determined as follows; green colour on AFI is considered as non neoplastic, purple as neoplastic, and the Kudo classification determines the prediction of histology when colour on AFI was ambiguous.To date 93 patients (39 male, mean age 52 yrs) have been included. Colonoscopy was performed with AFI first in 47 patients. In these patients 82 polyps (33 adenomas) were detected by AFI. Subsequent WLE detected 32 additional polyps (12 adenomas). In the 46 patients assigned to WLE first, 67 polyps (38 adenomas) were found. Subsequent AFI revealed 26 additional polyps (15 adenomas). The sensitivity of AFI for the primary detection of adenomas was 73% versus 72% for WLE (p=1.0). The sensitivity and specificity of the Kudo classification by NBI for predicting histological outcome were 80% and 68% respectively. When AFI colour was taken into account next to the Kudo classification, sensitivity and specificity were 87% and 69% (compared to the Kudo classification alone; p=0.136).Conclusion: Our preliminary results suggest that the sensitivity for the detection of adenomas is similar for WLE and AFI. The sequential use of both techniques improves the detection of adenomas. The additional assessment of AFI colour improves the accuracy of the Kudo classification by NBI for the prediction of histopathological outcome.

**Endoscopic Tri-Modality Imaging improves the detection of high-grade dysplasia and early cancer in Barrett's esophagus; an international multi-center feasibility study.**

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Introduction: Video autofluorescence imaging (AFI) may improve the detection of early neoplastic lesions in Barrett's esophagus (BE) but is associated with a high false-positive rate. Detailed inspection of AFI suspicious areas with narrow band imaging (NBI) may reduce this false-positive rate of AFI. Endoscopic Tri-Modality Imaging (ETMI) incurporates high-resolution endoscopy (HRE), video autofluorescence imaging (AFI) and narrow band imaging (NBI) in a single device with magnification in the HRE or NBI mode. This study investigated the diagnostic potential of ETMI and the relative contribution of each modality for the detection of high-grade dysplasia (HGD) or early cancer (EC) in BE.
Methods: 60 BE pts were examined with the ETMI system: 22 were referred for endoscopically inconspicuous HGD/EC, 5 underwent follow-up after endoscopic treatment, and 33 participated in a regular BE surveillance program. The esophagus was first inspected with HRE followed by AFI for the detection of additional lesions. All lesions detected with HRE and/or AFI were subsequently inspected by NBI. Biopsies were obtained from all suspicious lesions for blinded histopathological assessment followed by random biopsies according to the Seattle protocol. Results: Per patient: 19 pts were diagnosed with HGD/EC; 9 pts (47%) had lesions detected during the initial inspection with HRE (13 lesions in 9 pts) and three of these 9 pts had additional areas detected during inspection with AFI that were not seen with HRE; 8 pts (42%) had no visible abnormalities on HRE and were diagnosed with AFI only; 2 pts (11%) had HGD detected in random biopsies only.Per lesion: During inspection with HRE 36 suspicious lesions were detected; 13 contained HGD/EC (false positive rate HRE: 64%). All these 13 lesions were suspicious on AFI. After HRE inspection, AFI detected an additional 78 lesions; 14 contained HGD/EC (false-positive rate of AFI after HRE: 82%). Detailed inspection with NBI, reduced this false positive rate to 24%, but 2 lesions (3%) containing HGD were classified as not being suspicious with NBI.
Conclusion: In this international multi-centre study, AFI improved the detection of HGD/EC in BE from 47% to 89% and detected additional lesions in 33% of patients identified with HRE. AFI was associated with a false-positive rate of 82%. Detailed inspection with NBI improved the false-positive rate of AFI to 24% at the expense of misclassifying 2 lesions with HGD as being not suspicious.

## Radiofrequency Ablation of Barrett's Esophagus Containing High-Grade Dysplasia

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Circumferential ablation of non-dysplastic Barrett's esophagus (BE) has been proven as safe and effective. This study assessed the efficacy and safety of ablation for BE with high-grade dysplasia (HGD) in patients with and without prior endoscopic resection (ER).
Eligible patients showed BE with HGD on at least 2 prior EGDs. Visible abnormalities were resected prior to ablation. Persistence of dysplasia was confirmed with biopsy after ER. Patients received esomeprazole 40 mg BID during study.
A balloon-based electrode (HALO$^{360}$ System) was used for primary circumferential ablation (CA) and an endoscope-mounted electrode (HALO$^{90}$ System) for secondary focal ablation (FA) of residual BE. Both systems (BÂRRX Medical, Sunnyvale, CA) use an electrode array that delivers a short burst of high power RF energy (40 W/cm$^2$) at a preset energy density (12 J/cm$^2$).
After primary CA, EGD was performed at 2 mo intervals with secondary ablation of residual BE using CA or FA, depending on extent of BE. Two mos after the last ablation, EGD with Lugol's and large cup biopsy (4Q/q 1cm) was performed. Histopathology was reviewed by a single pathologist. Primary endpoint: complete response dysplasia (CR-D), absence of dysplasia in all biopsies. Secondary endpoints: adverse events (AE); visible BE regression; complete response intestinal metaplasia (CR-IM), absence of IM in all biopsies.
Twenty-three pts (17 men, median age 66 yrs, IQR 55-78) were treated (median BE length 7 cm, IQR 4-10). ER was performed in 13 patients: mucosal carcinoma (n=4), HGD (n=6) and LGD (n=3). Worst pathological grade of BE after ER and prior to RFA was LGD (n=3) and HGD (n=20).
Patients underwent a mean of 1.5 CA and 2.6 FA sessions. CR-D was achieved in 22/23 patients (96%) and CR-IM in 21/23 patients (92%). Patients with residual BE (n=2) have only small islands remaining (median BE regression: 99%). There were 3 AE's. Fever/chest pain (n=2) after CA, resolved with narcotics. An ER-related stenosis (n=1), resolved after 1 dilation. There were no thermally-mediated strictures. After a median additional follow-up of 6 mos and 2.1 endoscopies, no patient with CR-D has shown recurrence of dysplasia and no patient with CR-IM has shown recurrence of IM. None of the 521 biopsies of neosquamous mucosa contained subsquamous BE.
Radiofrequency ablation of BE containing HGD is a safe and effective treatment, with a CR-D and CR-IM of 96% and 92%. RFA can be safely performed after prior ER for visible abnormalities.

**Stepwise radical endoscopic resection for complete removal of Barrett's esophagus with early neoplasia: a prospective study of 56 patients with 2 years follow-up**

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Aim of this study was to prospectively study the use of stepwise radical endoscopic resection (SRER) of Barrett's esophagus (BE) with early neoplasia.
After endoscopic work-up and review of all biopsies, patients with high-grade dysplasia (HGD) or early cancer (EC) in BE ≤ 5 cm, with no signs of submucosal infiltration or lymph node/distant metastases were included. SRER sessions (cap-technique or multi-band mucosectomy) were performed with 6 weeks intervals. If necessary, small islands of residual BE were ablated using argon plasma coagulation (APC). Follow-up (FU) with lugol-staining and jumbo biopsies was scheduled every 6 months, with EUS after 6 and 12 months, and yearly thereafter.
56 consecutive patients were included: 48 males, mean age 65 ± 9.0 yrs, median BE length 4 cm (IQR 2-5). Complete eradication of HGD/EC was achieved in all patients (100%) in a mean number of 3 ± 0.9 sessions. Histopathology revealed HGD in 26 and EC in 26 pts, all with free deep resection margins. Although revision of pre-treatment biopsies confirmed the pre-treatment diagnosis of HGD, 4 patients had no HGD detected in their resection specimens.
SRER resulted in complete removal of all BE in 44 (79%) patients: four (7%) had a small rim (<5 mm) of non-dysplastic residual BE in their distal esophagus, eight (14%, all had undergone APC) had small foci of BE buried underneath neosquamous mucosa (in general only in 1-2 biopsy specimens and not reproduced during further FU).
Complications occurred in 4/165 (2%) endoscopic resection procedures: one asymptomatic perforation, and three delayed bleedings. Symptomatic stenosis occurred in 24/58 (41%) patients and was effectively treated by endoscopic bougienage (median number dilatations 4 (IQR 2-5)).
Median FU was 24 mo (IQR 19-32). There were no deaths. One patient (2%) had a 2-mm island of HGD detected after 17 mo FU that was resected endoscopically. Two pts (5%) had a small rim (<5 mm) of non-dysplastic BE detected in their distal esophagus.
Conclusions: Stepwise radical endoscopic resection is effective for eradication of early BE neoplasia with a low recurrence rate during FU. A significant number of patients, however, develop symptomatic stenosis. Complete eradication of all BE is achieved in the majority of cases with only minute, non-dysplastic remnants of IM in those with persistent or recurrent BE.

**New design stents for the palliation of dysphagia in patients with irresectable esophageal or gastric cardia carcinoma: a randomized study**

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Stents are commonly used for the palliation of obstructing esophagogastric cancer. One of the drawbacks of the presently used stents is the high percentage of recurrent dysphagia due to stent migration and tissue in- or overgrowth. New stents have been designed to overcome this unwanted sequel of stent placement. The aim of this study was to compare the Ultraflex stent (Boston Scientific, Natick, USA), with the newly designed Polyflex stent (Boston Scientific), and the Niti-S stent (Taewoong Medical, Seoul, Korea) in patients with inoperable carcinoma in the esophagus or gastric cardia.Between June 2004 and May 2006, 125 patients were randomized to treatment with an Ultraflex stent (n=42), Polyflex stent (n=41) or Niti-S stent (n=42). Patients were followed by scheduled telephone calls at 14 days after treatment, and then monthly for 6 months or until death. Recurrence of dysphagia, technical and functional outcome, and complications were analyzed with Kaplan-Meier curves and log rank testing. Quality of life was assessed by EORTC QLQ C30 and EORTC OES18 questionnaires.Technical problems occurred in 9 (7%) patients, mainly with Polyflex stents (n=7). Dysphagia improved from a median score of 3 (liquids only) to 1 (ability to eat some solid food) in all 3 stent groups. There were no differences in complications between the 3 devices. Recurrent dysphagia occurred more frequently with Ultraflex stents (p=0.03), and was caused by tissue growth (Ultraflex stent 13/42 (31%) vs. Polyflex stent 4/41 (10%) vs. Niti-S stent 10/42 (24%)), stent migration (Ultraflex stent 7/42 (17%) vs. Polyflex stent 12/41 (29%) vs. Niti-S stent 5/42 (12%)), and food bolus impaction (Ultraflex stent 10/42 (24%) vs. Polyflex stent 2/41 (5%) vs. Niti-S stent 1/42 (2%)). No differences were found in general and disease-specific quality of life scores between the 3 stent types.Conclusions: All 3 stents are safe and offer the same degree of palliation from malignant dysphagia. The new stents have the advantage that reinterventions are less frequently needed, as the Polyflex particularly reduces tissue growth and the Niti-S stent migration rates. It may well be that recurrent dysphagia could be even more reduced by designing a stent that combines the non-metal material used for the Polyflex stent with the anti-migration wire of the Niti-S stent.

**Efficacy of a new nitinol enteral stent (WallFlex) in malignant gastric outlet obstruction: a prospective, open, multicenter clinical trial**

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Gastric outlet obstruction (GOO) is a late complication of advanced gastric, periampullary and duodenal malignancies. Palliation of symptoms of obstruction is the primary aim of treatment in these patients. Self-expandable metal stents (SEMS) have emerged as a promising treatment option. The aim of this prospective multicenter study was to investigate the efficacy of a new enteral stent (WallFlex™, Boston Scientific, Natick, MA, USA) in patients who had symptoms from malignant gastro-duodenal obstruction due to incurable distal gastric, periampullary or duodenal malignancy. Consecutive patients who fulfilled the patient selection criteria and presenting at one of the participating hospitals between January 1st 2005 and February 1st 2006 were included. In case of biliary obstruction, adequate drainage of the biliary tree with metal stents was achieved prior to stenting. Patients' characteristics, severity of obstruction (symptoms and GOOSS-score (GOO-Scoring System)), general condition (Body Mass Index (BMI) and WHO performance status), additional therapy (chemotherapy, radiotherapy) and quality of life questionnaires were collected prior to enteral stent placement. Procedure-related data were recorded by the treating physician. Follow-up data were prospectively collected by telephone on a two-weekly basis, until the patient died. Study endpoints were: technical success (successful stent placement and deployment), clinical success (relief of symptoms and/or improvement of GOOSS-score) and intervention-related complications. A total of 51 patients were included (25 male, mean age 69 years). The main cause of GOO was pancreatic cancer (35 patients, 69%). All procedures were technically successful. Clinical success was achieved after 1 week in all but 5 patients. The GOOSS-score improved significantly (Wilcoxon signed ranks test-two-sided; $p<0.0001$) when comparing the score prior to stenting with the mean score during the remainder of their lives. Oral intake was resumed at a mean of 1 day (0-9 days) after stent placement. The median survival was 63 days (interquartile range 121 days). There were 7 stent-related complications (migration n=2, tumor ingrowth n=4, enteral stent obstruction due to distal migration of the biliary stent n=1) in 5 patients. This single-arm prospective cohort study shows that in patients with non-resectable malignant GOO placement of a WallFlex enteral stent is safe and provides a significant relief of obstructive symptoms.

**EUS-Guided trucut biopsy versus EUS-guided fine needle aspiration; an evaluation of 67 patients with mediastinal lesions.**

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Endoscopic ultrasound guided fine needle aspiration (EUS-FNA) is a sensitive method to obtain cytological specimen from solid lesions in close proximity to the gastrointestinal tract. Whilst FNA provides cells for analysis, large-calibre tru-cut biopsy (EUS-TCB) needles give specimens that can be used for histopathological analysis as well. We assessed the additional diagnostic yield of EUS-TCB in patients with solid mediastinal lesions in whom EUS-FNA was performed.In the period from July 2003 to November 2006, 67 patients with mediastinal lesions, accessible to EUS-FNA and EUS-TCB, were included in the study. In all patients, a mean of three passes of EUS-FNA (EchoTipUltra 22 GA) was followed by EUS-TCB using the Quick-Core (19GA) biopsy needle. Cytological and histological specimen were evaluated by two pathologists, blinded for patients' condition. A final diagnosis was obtained by combining all information present (EUS-FNA & EUS-TCB results, mediastinoscopy, bronchoscopy (if performed) and other investigations).Mean size of the lesions investigated was 23.7 ± 13.6 x 43.1 ± 14.3 mm. A total of 72 biopsies were obtained. No puncture related complications were encountered. The final diagnosis consisted of sarcoidosis (38%), non-small cell lung cancer (5%), small cell lung cancer (7%), TBC (3%), and miscellaneous (47%). The diagnostic accuracy of EUS-FNA and EUS-TCB was 90% and 83% respectively (P>.05). In EUS-FNA-negative patients, EUS-TCB provided a final diagnosis in an additional 4 patients (6%), whereas EUS-FNA was positive in 5 EUS-TCB negative patients (7%). In 4 (6%), both FNA and TCB were inconclusieve. Conclusion: The diagnostic yield of EUS-FNA and EUS-TCB is comparable. EUS-TCB can provide additional information leading to a final diagnosis in a subset of patients in whom EUS-FNA is negative.

## Endoscopic treatment of bile duct injury: long term outcome and predictors for success

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Background: Endoscopic stent therapy is widely accepted as initial treatment modality for postoperative bile leakage and/or bile duct strictures after laparoscopic cholecystectomy. Although, reliable factors for predicting success would be useful, they are unreported.Aim: To analyze outcome of endoscopic stent therapy after BDI, to identify factors predicting successful outcome of stent therapy for bile duct strictures, and to determine the effect of sequential insertion of multiple stents for strictures.Methods: Between 1990 and 2006, 203 patients underwent stent therapy for BDI. From a prospective database two groups of patients were composed: patients with bile duct leakage (n=93) and patients with a bile duct stricture (n=110).Results: Minor stent related complications occurred in 12 patients (13%) with bile duct leakage. Median duration of stenting was 1.5 months (range 1-11). One patient was referred for surgery, 3 patients (3%) developed a stenosis after stricture free interval, and one patient died due to a BDI related cause. The overall success rate was 96% (n=89). In patients with a bile duct stricture minor stent related complications occurred in 33% (n=36)). The median duration of stenting was 11 months (range 1-69) with a median number of stents of 2 (1-7). Subsequent surgery was indicated in 22 patients (20%),6 patients (6%) developed a stenosis after stent removal, and two patients (2%) died due to a BDI related cause. After a mean duration of follow-up of 4.5 years liver function tests did not show signs of occult bile duct strictures. The overall success rate was 74% (n=81). In patients treated for a stricture the independent predictor for success was the number of stents inserted during the first procedure (Odds ratio [OR]=2.9 per stent, 95% confidence interval [CI] =1.1-8.2, p=0.04). Independent predictors for failure were injuries classified as Bismuth III (OR=0.12, CI=0.02-0.91, p=0.04) and IV (OR=0.04,CI=0.003-0.55,p=0.02), and endoscopic stenting before referral (OR=0.23,CI=0.06-0.87,p=0.03). After the introduction of multiple stent therapy, the overall success did not improve (before 77% vs. after 66%, p=0.25), while more patients reported stent related pain (before 11% vs. after 28%, p=0.02).Conclusions: Endoscopic stent therapy is associated with excellent outcome in patients treated for postoperative bile duct leakage and strictures. However, the benefit of multiple stent therapy is not readily apparent in this cohort.

**Endoscopic ultrasonography: a valuable tool in screening high-risk patients for pancreatic cancer**

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Introduction: of all pancreatic cancers (PC) 5-15% is considered to be familial or hereditary in origin. Despite improvement in imaging and surgical therapy, overall prognosis of PC remains dismal. Five-year survival in patients after curative surgery is no more than 10%. Early detection of cancer and especially premalignant lesions could improve outcome. Unfortunately abdominal ultrasound, ERCP, CT scan and MRI have proven to be of very limited value for screening in high-risk patients. Endoscopic ultrasonography (EUS) could be a valuable tool in screening as it enables the endoscopist to examine both pancreatic parenchyma and pancreatic duct in detail. Furthermore, cytological specimens can be obtained safely and accurately. Drawbacks however are that EUS is considered an invasive procedure and that it is highly operator dependent.
Methods: since 2005 patients with familial or hereditary PC were offered EUS screening. Procedures were carried out under conscious sedation and performed by an experienced endoscopist. An electronic linear echoendoscope was used in all procedures. When abnormalities were found, EUS was followed by CT and/or MRI.
Results: 20 patients from 14 families (M/F 10/10) were screened. Genetic background was diverse: patients with at least two first-degree relatives with PC (familial PC, n=10), patients with familial PC and/or familial atypical multiple mole melanoma syndrome (FAMMM) with unclassified variants (UV) in the p16 gene (n=5), Peutz-Jeghers syndrome (n=2), genetically proven FAMMM syndrome (n=4)and one carrier of a pathogenic BRCA2 mutation in a family with familial PC. No procedure related complications occurred. Significant pathology was found in three patients (15%): in a patient with a p16 UV multifocal side-branch intraductal papillary mucinous neoplasms (IPMN) were found, all less than 1,5 cm. in size. In a patient with familial PC one side-branch IPMN of 5 mm was found. Furthermore, one small pancreatic tail cancer (22 mm) in an asymptomatic BRCA2 carrier was found. Conclusions: EUS screening is feasible and has a significant yield in selected high-risk patients.Whether this improves outcome in these patients remains to be proven.

## Endoscopic ultrasound guided transmural debridement of symptomatic organized pancreatic necrosis

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Pancreatic necrosis is a severe complication of acute pancreatitis. Surgery has been the mainstay of treatment once intervention is necessary. Surgical management is however associated with significant morbidity and mortality. By the time necrosis becomes organized endoscopic therapy has the potential to offer an alternative treatment. However, due to rapid blockage of stent or naso-cystic catheter by necrotic material, endoscopic drainage of pancreatic necrosis is often considered contraindicated. This could be overcome by adding endoscopic debridement to transmural drainage. We have performed a retrospective study on our prospectively collected cohort of patients evaluating the results and complications with this new technique. Aim was to evaluate its safety and efficacy and to identify procedural aspects that may improve outcome.All consecutive patients who underwent endoscopic debridement of pancreatic necrosis in our hospital between January 2003 and July 2006 were included. In all patients the treatment was started with EUS-guided transmural drainage of the collection with placement of multiple stents and naso-cystic catheter. The next step consisted of balloon dilatation up to 18 mm, advancement of an endoscope into the retroperitoneal cavity and endoscopic debridement of the collection under direct vision. Endoscopic debridement was repeated every 2 days until most necrotic material was evacuated. Additionally, naso-cystic catheter irrigation was performed manually with saline 6-8 times a day. 25 patients were identified (13 women, 12 men), who had undergone debridement of 27 collections. After the initial stent placement, in 11 collections (41%) one, in 13 (48%) two, in 2 (7%) three and 1 (4%) four endoscopic debridement procedure(s) were performed. There was no mortality. Complications occurred in 2 patients (7%) and required surgery: Hemorrhage in one case and perforation of cyst wall in the other. During a median follow up of 16 (range 3-38) months, the overall clinical success rate with resolution of the collection and related symptoms was 93%. Two patients (7%) developed an asymptomatic recurrent pseudocyst of 5.6 and 3 cm.
Conclusion: In this study we have shown that endoscopic debridement is an effective and relatively safe minimally invasive therapy in patients with symptomatic organized pancreatic necrosis. Further comparative studies need to define its definitive role in the management of these patients.

**Why do subjects decline colorectal cancer screening by FOBT?**

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The colorectal cancer screening pilot-study in the Netherlands will invite 20.000 individuals by sending them a fecal occult blood test (FOBT). Overall, participation rates for CRC are low (30-60%). To increase participation it is important to identify the reasons why individuals do not participate. Targeting specific subgroups could lead to higher participation levels. Our primary aim was to identify motivations of non-participants to the Dutch FOBT screening program. The second aim was to identify which motivations could be targeted for increasing adherence.We randomly selected 1000 invited individuals of the Dutch screening program. In the group of non-participants, telephone interviews were conducted 3 to 6 months after the initial invitation if a listed telephone number was available. In the interview we asked for the main reason for non-participation. The answers were divided in two groups: Group A reasons that could possibly be influenced by extra attention or education; Group B seemingly non-reversible motivation. Of the first 1000 invited individuals 49.6% were non-participants. Of the non-participants 215 had a listed telephone number. In total 131 non-participants were reached and within this group a interview was conducted. In this group 20 non-participants, when called, stated they were reminded by the phone call and were planning to perform the FOBT soon. Thus, an increase in participation of 15% could be seen by a single telephone call. The main reasons of the remaining 111 non-participants were divided in A and B.
Group A (seemingly possible to influence, 60%): no reason to participate because of no complaints (11%), did not read information (11%), disgust of performing FOBT (9%), not interested (9%), too busy (5%), anxiety (2%), on vacation (2%), too much information (2%), concern about privacy (2%), no reason (7%). Group B (seemingly non-reversible, 40%): too ill to perform FOBT (11%), family problems (e.g. ill spouse) (9%), fatalism (6%), recently received colonoscopy (6%), rectal blood loss (consulted GP) (4%), and others (4%). Conclusion: In this preliminary study 60% of non-responders declined screening because of reasons that could possibly be influenced by supplying more or better information. Targeting these factors predicting non-compliance with specific measures could lead to an increased participation rate. Further research will be necessary to see whether adherence increases indeed once specific measures have been taken.

**The incidence of hereditary non-polyposis colorectal carcinoma related cancer in clinically ascertained MLH1, MSH2 and MSH6 families**

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Hereditary non-polyposis colorectal carcinoma (HNPCC) is caused by mutations in the mismatch repair genes (MLH1, MSH2, MSH6) and is responsible for 2-5% of all colorectal cancer (CRC) cases. Few series have suggested that MSH6 mutation carriers develop CRC at a higher age and have a higher incidence of endometrial cancers (EC) compared with MLH1 or MSH2 mutation carriers, however, data are limited. The aim of the present study was to evaluate the phenotypic manifestations of MSH6 families compared to MLH1 and MSH2 families.Data were collected from medical records and family pedigrees of HNPCC families with a proven mutation in the MLH1, MSH2 or MSH6 gene. Affected subjects were included if the tumor diagnosis was confirmed by histology or clinical reports. Clinical data of MSH6 families were compared with data from families with MLH1 and MSH2 mutations.A total of 68 HNPCC families with a mutation in MLH1 (n=25 families, including 1361 individuals), MSH2 (n=23, including 1579 individuals) or MSH6 (n=20, including 2023 individuals) were identified. CRC was less frequently observed in MSH6 families (mean: 2.5 cases CRC/family) compared to MLH1 (mean: 3.1 CRC/family), and MSH2 families (mean: 2.8 cases CRC/family), $p< 0.01$. The mean age of CRC onset was significantly higher in MSH6 families (mean 58 ± 14 years) compared to MLH1 (mean 48 ± 13 years) and MSH2 families (mean 47 ± 13 years), $p < 0.01$. Endometrial cancer developed more often in MSH6 families than in MLH1 or MSH2 families (mean 1.6 cases/family vs. 0.7 cases/family, $p< 0.01$). The age of EC onset was significantly higher in MSH6 families (mean age: 55 ± 9 yrs) compared to MSH2 (mean 45 ± 10 yrs, $p<0.01$), but not to MLH1 families (mean age: 51 ± 14 yrs). Small bowel tumors were significantly more frequently observed in MSH2 families than in MSH6 families (6% vs. 0%, $p<0.01$). Urothelial cell carcinoma was more often diagnosed in both MSH2 (5%) and MSH6 (5%) families compared to MLH1 (1%, ns). There was no difference in frequency of ovarian, brain and skin tumors among the HNPCC families. Conclusions: MSH6 mutation carriers develop both CRC and EC at a older age than MLH1 or MSH2 mutation carriers. EC is more frequently observed in MSH6 families, while small bowel tumors are more frequently observed in MSH2 families. This finding emphasizes the importance of individualized programs (i.e. colonoscopy and periodical gynaecological examination) in MSH6 families as well as in MLH1 and MSH2 families.

**The use of genetic testing in (attenuated) familial adenomatous polyposis families**

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Genetic testing can be used to identify persons at risk for familial adenomatous polyposis (FAP) prior to the development of polyps. Subjects with a mutation can be appropriately managed with prophylactic colectomy and endoscopical screening, while subjects without a mutation can be dismissed from further surveillance. The aim of the present study was to determine the use of genetic testing in (attenuated)FAP families with a known mutation in the APC or MUTYH gene.Data were collected from medical records and family pedigrees of patients originating from (A)FAP families. Pre-test genetic risk in families with an APC mutation was defined as 100% (diagnosed with polyposis +/- colorectal cancer), 50% (first degree relative with polyposis +/- colorectal cancer or a mutation) and 25% (parent with a 50% risk). The test rate in parents and siblings of apparently de novo APC mutation carriers was also evaluated. In the MUTYH families pre-test genetic risk was defined as 100% (diagnosed with attenuated polyposis +/- colorectal cancer) and 25% (a sibling with a 100% risk or a mutation).Forty-two families with a known mutation in APC (n=34) and MUTYH (n=8) were included in the study. The 34 APC families consisted out of 287 living subjects aged 10 years or older (53% male) with a 100% (n=46), 50% (n=102) or 25% (n=57) pre-test genetic risk of carrying the family specific mutation and parents (n=34) or siblings (n=48) of an apparently de novo mutation carrier. Genetic testing was used by 120 (42%) subjects, a family-specific mutation was detected in 50 (42%) of them. Of the subjects with a pre-test genetic risk of 100%, 50% or 25% for carrying the mutation, respectively 93%, 45% and 5% used genetic testing ($p< 0.01$). The 8 MUTYH families consisted out of 30 living adult subjects (47% male) with a 100% (n=8) and 25% (n=22) pre-test genetic risk. Genetic testing was used by 16 (53%) subjects and a mutation was detected in 13 (81%) of them. All of the 100% risk carriers used genetic testing compared to 36% of the 25% risk carriers ($p<0.01$). Conclusions: There is considerable interest in genetic testing in (A)FAP families, however many risk carriers still refrain from testing. This may have implications for the prevention of cancer by prophylactic colectomy or endoscopic surveillance. Methods for improved implementation of genetic testing should be studied and optimal testing should be used as a part of the standard medical care for subjects at risk for (A)FAP.

**Induction of caspase-8 and cFLIP expression during colorectal carcinogenesis in sporadic and HNPCC adenomas and carcinomas**

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TNF-Related Apoptosis Inducing Ligand (TRAIL) is a promising agent for the induction of apoptosis in neoplastic tissues. Death receptors DR4 and DR5, to which TRAIL binds, are strongly upregulated in colorectal adenomas and carcinomas. Important determinants of TRAIL sensitivity are two intracellular proteins of the TRAIL pathway, caspase-8 and its anti-apoptotic competitor cellular Flice-Like Inhibitory Protein (cFLIP). Little is known about the expression of these two proteins in colorectal tissues. The aim of this study was to investigate basic expression levels of caspase-8 and cFLIP in normal colorectal epithelium (n=20), colorectal adenomas (n=66) and colorectal carcinomas (n=44) using immunohistochemistry to assess changes in expression levels during carcinogenesis. Since the carcinogenic pathways in sporadic cancers and in cancers associated with the hereditary cancer syndrome Hereditary Non-Polyposis Colorectal Cancer (HNPCC or Lynch syndrome) are markedly different, both sporadic and HNPCC-associated adenomas and carcinomas were studied. Expression of both caspase-8 and cFLIP was similar in cases with sporadic and hereditary origin. Expression of caspase-8 in colorectal adenomas and carcinomas was increased when compared to normal colon tissue ($P = 0.017$). Nuclear, paranuclear as well as cytoplasmic localizations of caspase-8 were detected. Immunohistochemistry revealed an upregulation of cFLIP in colorectal carcinomas in comparison to normal epithelium and colorectal adenomas ($P < 0.001$). No correlation between expression levels of caspase-8 and cFLIP was observed. The caspase-8/ cFLIP ratio varied strongly between the individual adenomas and carcinomas. In conclusion, both caspase-8 and cFLIP are upregulated during colorectal carcinogenesis. Upregulation of caspase-8 may be an interesting approach to maximize TRAIL sensitivity in colorectal neoplasms, whereas downregulation of cFLIP is an alternative for those colorectal neoplasms in which a low caspase-8/ cFLIP ratio is an important determinant of TRAIL sensitivity.

## Redesigning the process of colorectal cancer care: impact on quality of care and cost

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After the endoscopic finding of colorectal cancer (CRC), patients usually are worked up for surgery and possibly (chemo-)radiotherapy. The CRC care process involves many doctor visits and many diagnostic and therapeutic procedures. This complexity may lead to redundancies or omissions in the CRC care process. We analyzed the CRC care process and implemented changes to optimize its quality.
Materials and Methods: A retrospective analysis of 100 CRC cases was done (waiting times, number of outpatient visits, diagnostic/therapeutic procedures, in hospital length of stay (LOS) and complications), including a financial analysis. A multidisciplinary expert group defined which diagnostic and therapeutic procedures were essential. The group developed a fast track procedure in order to omit redundant and nonessential procedures and reduce the number of hospital visits. In depth interviews with patients defined psychosocial needs in the CRC care process. An enhanced postoperative recovery program was implemented. The function of a case manager was instituted. The case manager had tasks both at the patient level and at the organizational level. She was present at all patient's hospital visits and was available for additional questions or requests. Also she was responsible for coordination of the process. Goals were set with respect to time from endoscopy to surgery, number of hospital visits, in hospital LOS, total costs and patient satisfaction, both in patients with colon cancer (CC) and rectal cancer (RC).
Results: In CC time from endoscopy to surgery: prior to start program, goal and after implementation (n=40) was resp 40, 14, 10 days. In RC time from endoscopy to surgery was resp 55, 40, 36 days (n=10). LOS in CC was resp 10, 6, 8 days, in RC resp 12, 8, 10 days. Number of hospital visits in CC resp 8, 4, 4, in RC 12, 6, 6. Goals and actual reduction in cost per patient in CC were Euro 1365 resp 830, in RC Euro 817 resp 405. Patient satisfaction was significantly increased. A similar approach for an esophageal cancer care process is being started.
Conclusion: A structured multidisciplinary approach to optimize complicated care processes can significantly increase quality of the process and simultaneously reduce costs. A case manager to coordinate and monitor the process is essential and cost effective. Once this type of approach has been instituted, it can easily be transplanted to optimize other complicated care processes.

**DNA copy number profiles of primary colorectal cancers as predictors of response to therapy**

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Colorectal cancer is biologically a heterogeneous disease, which gives rise to differences in clinical behavior, including risk of metastasis and response to drug therapy. Obviously, the success of both classical drug therapies as well as novel targeted therapies can be improved by matching the right combination of drugs with different biological classes of CRC.The aim of the present study was to correlate genome wide DNA copy number status in advanced colorectal cancer with response to systemic chemotherapy.Thirty-two patients with advanced colorectal cancer were selected from the patient series of the CAIRO study of the Dutch Colorectal Cancer Group (DCCG), based on either a good (n=17) or a poor response (n=15) to first-line combined irinotecan and capecitabine therapy. For all cases, DNA was isolated from formaldehyde-fixed paraffin embedded tissue samples of the primary tumors.High resolution DNA copy number profiles were determined by means of 30k oligonucleotide-based array comparative genomic hybridization (array CGH).The group of the non-responders had fewer aberrations (P = 0.04) than the responders, especially for the losses (P = 0.01). The average number of chromosomal alterations per carcinoma in the group of the 17 responders was 8.9 (range 1-17), with a mean number of 4.1 gains (range 0-9) and 4.8 losses (range 0-11). For the group of the 15 non-responders the average chromosomal aberrations was 5.2 (range 0-13), with a mean number of 3.7 gains (range 0-11) and 1.5 losses (range 0-7). The striking difference in aberrations between the two groups were losses of 1p36 (P = 0.05), 18p (P = 0.02), and 18q (P = 0.01), that were more frequent in the CRC of patients which had a good response to chemotherapy.Hierarchical cluster analysis of the array CGH data revealed two clusters with cluster 1 containing twenty-one tumors and cluster 2 eleven tumors. Fifteen out of twenty-one tumors of cluster 1 consisted of responders, while in cluster 2 nine out of eleven tumors were non-responders. Cluster membership showed a significant correlation with response status (P = 0.01). In conclusion, primary tumors of patients with advanced colorectal cancer with a good or poor response to systemic chemotherapy show different DNA copy number profiles. Tumors of patients with a good response to combined irinotecan and capecitabine treatment had overall more chromosomal aberrations, especially losses of 1p36, 18p and 18q.

**Performance characteristics of faecal occult blood tests: which test to use for colorectal cancer screening?**

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Introduction: Guaiac-based faecal occult blood tests (FOBT's) in a colorectal cancer screening setting are commonly hampered by a poor specificity and positive predictive value, resulting in many (futile) follow-up colonoscopies. Hence, immunochemical FOBT's with apparently better clinical performance, absence of dietary restrictions and only one faecal sample required have been proposed as a more efficient screening tool.
Aim: To compare an immunology-based (OC sensor®, Eiken Chemical Co, Japan) and a guaiac-based (hemoccult®, Beckman Coulter, Inc. USA) FOBT in consecutive patients undergoing colonoscopy in terms of clinical yield of colorectal cancer and advanced adenomas.
Methods: All patients aged > 18 years and scheduled for a colonoscopy in participating hospitals (N=3) were asked to perform both FOBT's in the week prior to colonoscopy. A haemoglobin concentration of > 100 ng/ml in the test sample was considered a positive result. The McNemar's test was used for the comparison of correlated proportions. $P<0,05$ was considered statistically significant
Results: After excluding 70 patients, in whom the caecum was not visualized and/or bowel cleansing was insufficient, the total number of eligible patients was 446. The overall positivity rates were 7,4% and 10,3% for the hemoccult® test and OC sensor® test, respectively. Colorectal carcinoma and advanced adenomas (i.e., polyps ≥ 1 cm and/or villous architecture and/or high-grade dysplasia) were found in 2,5% and 9,6% of the patients, respectively. Small adenomas, colitis and other lesions were identified in 57% of the patients. No lesions were found in 31% of the patients. Test characteristics for both FOBT's are shown in Table 1. Non of the differences observed were statistically significant.
Conclusions: Although the sensitivity and specificity of both tests in detecting colorectal cancer were rather high in this patient group, the sensitivities were only modest/poor in detecting high-risk, pre-cancerous lesions. Moreover, the low positive predictive values might hamper the introduction of either one of these tests in a screening setting. Particularly, the immunological FOBT did not improve the overall positive predictive value. A larger cohort is currently being investigated to confirm these preliminary findings.

## Development of an RNA-based fecal screening panel test for colorectal cancer

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Many Western countries have adopted screening for colorectal cancer using a non invasive fecal occult blood test (FOBT). Blood as a biomarker is not specific for colorectal cancer and leads to a relatively high percentage of false positives and lack of sensitivity and specificity for early lesions. DNA, protein, or RNA from exfoliated colonocytes in stool are potentially both more sensitive and specific than blood as a marker for CRC. A commercial test involving the detection of tumour specific DNA has been developed, but is complex and expensive involving separate assays for each possible mutation in a panel of genes. In contrast, the detection of RNA markers of CRC only needs one assay, and can be adapted to detect multiple different markers simultaneously by multiplex PCR. It is thus potentially more amenable to automation, simpler and cheaper. The aim of this study was to assess reverse transcription-PCR assay methodology originally developed for the detection of entero-viruses, for the detection of colorectal cancer. This non invasive test can be used as a RNA based fecal test for CRC screening. RNA was isolated from 20 stool samples, 10 with CRC and 10 without. RT-PCR was performed using primers specific for seven of the most highly upregulated genes in CRC as found by SAGE analysis. Methodology developed and patented in our hospital for the detection of entero-viruses (M. Beld, et al., J Clin Microbiol, 2004) was used for improved RNA extraction and neutralization of inhibitors of PCR found in feces. This RT-PCR is a non-nested and fast assay. All assays included a negative control. The results were sequenced to confirm specificity for marker-RNA.Decay Accelerating Factor (DAF) was detected in 7/10 CRC stools; Cyclooxygenase II (COX-II) mRNA in 5/10 CRC stools; Dipeptidase-1 (DPEP-1) in 3/10 CRC stools. Other tested markers (MIC-1, C-19, C-18, RID-2, IGF-II) were inconclusive. By combining DAF, COX-II and DPEP the sensitivity of this mRNA panel was 8/10 true positive CRC stools 80% and specificity was 2/10 false positive controls (80%) for finding CRC.
Conclusion: An easy to use RT-PCR protocol can successfully detect multiple mRNAs in feces with encouraging sensitivity and specificity for CRC when combined. These preliminary findings are promising for the future non-invasive detection of CRC, suggesting that by using a panel of different mRNA markers the sensitivity and specificity will increase beyond those attainable with the FOBT.

## Analytic sensitivity of faecal DNA testing for colorectal cancer

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Faecal DNA tests for colorectal cancer (CRC) hold great promise. Sensitivity of these tests usually is measured in percentage of cases with a colorectal cancer that have detectable DNA alterations in their faeces. Yet, the actual amount of tumor DNA present in faeces of a given patient is unknown, and consequently also the analytical sensitivity of faeces DNA based tests. The aim of this study is to evaluate the detection level of stool based DNA tests in terms of cells per quantity stool sample.A range of 100 to 750 HT29 cells were spiked to samples of 80 milligram taken from homogenized stool of a colonoscopy negative individual. Whole genomic DNA was isolated using the QIAamp DNA stool mini kit (Qiagen, GmbH, Hilden, Germany) Human DNA was detected using a human specific beta globin PCR. Nested MSP for promoter methylation of GATA4 was performed to specifically detect HT29 derived DNA, in order to determine the analytic sensitivity of the assay.Human DNA (beta globin) was detectable even in faeces samples without cells added, creating a background signal in all samples. Promoter methylation of GATA4, which is a specific feature of the spiked HT29 cells, was detected in spiked samples with down to 100 cells per 80 milligram of faeces.
In conclusion, against a background of human non-tumor DNA, and DNA from other sources like bacteria, tumor DNA can be detected with high specificity and sensitivity.

## Acid suppression normalizes the expression of mucosal repair associated genes in the esophageal epithelium of GERD patients

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Past studies aimed at addressing the effects of acid reflux on gene expression patterns in the esophageal epithelium concentrated on inflamed tissues.
We aimed to determine changes in gene expression in non-inflamed esophageal epithelium of GERD patients. Address the role of acid by means of 1) acid suppression, and 2) collection of biopsies at two levels in the esophagus. 20 GERD patients (10 M, mean age 52) with total 24-h acid exposure of 6-12% and SAP≥95% were selected from pH-metry referrals. Ten patients discontinued PPI treatment, ten took pantoprazole 40mg bid, both two weeks prior to sampling. Ten age/sex-matched healthy controls (HCs) were recruited. Biopsies were taken during upper GI endoscopy from non-inflamed mucosa 6 and 16 cm proximal to the squamocolumnar junction and used for gene expression profiling or for histological evaluation. Profiling was performed on Human Genome U133 Plus 2.0 arrays (Affymetrix). Genes exhibiting a fold change >1.4 (t-test p-value <1E-4) in patient groups compared to healthy controls were considered differentially expressed. Differential expression was confirmed by real-time RT-PCR. No endoscopic abnormalities were seen in HCs. Histology confirmed the absence of inflammation at all sites. In GERD patients taken off PPIs, 52 genes were up-regulated in the distal esophagus epithelium taking that of HCs as reference. Furthermore, 69 genes were up-regulated in proximal esophagus. An overlap of 37 genes was observed between those two sets. The majority of those genes was associated with cell-cell contacts and communication, cytoskeletal reorganization and repolarization, and suggested of an adaptation to a migratory phenotype. Genes encoding proteins with anti-apoptotic functions or protective roles against oxidative stress were also up-regulated in GERD patients off PPIs. Strikingly, gene expression profiles of GERD patients on PPIs and HCs were indistinguishable.
Conclusions: Excessive acid reflux causes superficial damage and stress response in non-inflamed areas of the esophageal mucosa of GERD patients. Upon acid exposure, epithelial cells activate mechanisms globally known as epithelial restitution to increase their chance of survival, e.g. up-regulation of anti-apoptotic, anti-oxidant and migration associated proteins. Acid suppression therapy normalizes gene expression patterns in the epithelial cells of GERD patients undergoing PPI therapy to the point of them being indistinguishable from those of HC.

## Adherence to gastroprotection and the risk of NSAID-related upper gastrointestinal complications

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Upper gastrointestinal (UGI) complications are a well recognized risk of NSAID treatment, requiring prevention in high risk patients. Adherence to gastroprotective agents (GPAs) in NSAID users is suboptimal. The aim of the study was to investigate the association between the level of adherence to GPAs and the risk of serious NSAID-related UGI complications in patients using non-selective NSAIDs (nsNSAIDS). A nested case-control study was conducted within a cohort of new nsNSAID users with at least one risk factor for a NSAID-related UGI complication, identified within the Integrated Primary Care Information database between 1996-2005. Cases with UGI ulcers or bleedings during NSAID use were matched to controls on age and calendar time. Adherence to GPAs was calculated as the proportion of NSAID treatment days covered (PDC) by a GPA prescription. The primary risk window was the most recent episode of NSAID use prior to the index date. Multivariate conditional logistic regression analysis was used to calculate adjusted odds ratios (OR) with 95% confidence intervals (95%CI). Within the study cohort of 26,307 nsNSAID users with at least one risk factor, we identified 119 patients (0.45%) with an UGI ulcer or bleeding during or within 60 days after stopping the nsNSAID use. Considering the most recent episode of continuous nsNSAID use prior to the index date, 14.9% of the nsNSAID users received GPAs. Of these, 71.0% had a PDC ratio >80% (full adherence), 22.0% PDC ratios between 20-80% (partial adherence) and 7.0% being non-adherent (PDC <20%). The risk of a serious NSAID-related UGI complication increased from 2.5 (95%CI: 1.0-6.7) in partially adherent persons to 4.0 (95%CI: 1.2-13.0) in those with a PDC <20%. Considering the PDC level as a continuous measure, the risk of a serious NSAID-related UGI complication increased with 16% (95%CI: 2-32%) with every 10% decrease in adherence. Excluding H2RA users that were not adequately dosed for the prevention of NSAID-related UGI complications (i.e. less than double dose), the risk was increased 2.7-fold in patients that were partially adherent and 4.5-fold in patients that were non-adherent.
Conclusion: There is a strong relationship between the level of adherence to gastroprotective medication and the risk of serious UGI complications in high-risk nsNSAID users. This underlines the need for adequate patient instruction regarding adherence to GPAs and/or the further development of fixed combination strategies.

**Step-down is equally effective as step-up as initial management of new onset dyspepsia in Dutch primary care**

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Treatment of dyspepsia constitutes an important workload for general practice, and brings about high costs. In spite of consensus statements and guidelines, the most effective empirical strategy for initial treatment of dyspepsia in primary care remains to be determined.We conducted a double-blinded randomized trial comparing step-up and step-down treatment strategies for initial management of patients with new onset dyspepsia in primary care. Patients were treated stepwise with antacids, H2-receptor antagonist, and proton pump inhibitor, or the other way around. Each step lasted 4 weeks and treatment only continued with the next step if symptoms persisted or relapsed within 4 weeks. Patients were followed for 6 month.One hundred fifty (48%) of the participating general practitioners randomly assigned 664 patients to step-up (n=341) or step-down (n=323) treatment between October 2003 and January 2006. The mean age was 47 years, 360 (54%) were female, and the majority was Caucasian (94%). The number of treatment steps used did not differ between the strategies and were respectively one, two, or all three treatment steps for 132 (39%), 84 (25%), and 118 (35%) patients assigned to step-up, and 149 (46%), 57 (17%), and 113 (35%) patients assigned to step down. After six months, 238 (71%) patients in step-up and 219 (70%) patient in step-down reported sufficient symptom relief.Step-down is equally effective at 6 months as step-up for initial treatment of dyspeptic patients in general practice.

**Proton pump inhibitor use increases the risk of severe community-acquired infections.**

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Proton pump inhibitor (PPI) use has been associated with an increased risk of pneumonia and Clostridium difficile infections, presumably secondary to loss of the natural antibacterial host defenses provided by gastric acid. The relationship between PPI use and other serious infections remains uncharacterized.The aim of this study was to determine whether the use of PPIs increases the risk of severe community-acquired infections in a large population-based health utilization dataset. We conducted a population-based case-control study using a comprehensive health utilization database from the Canadian province of Manitoba. We identified current and prior users of PPIs admitted to hospital with severe community-acquired infections between 1995 until 2004. Up to 10 controls were matched on sex, year of birth, and index date. Conditional logistic regression was used to estimate the relationship between active use of PPIs and serious community acquired infections. We identified 119,047 PPI users of whom 904 met our diagnostic criteria for severe community-acquired infections. Patients with severe infections were 1.62 times more likely than controls to be actively using PPIs (95% Confidence Interval (CI):1.38-1.90). The association more pronounced in high-dose PPI users. Both respiratory (OR 1.78 (95% CI:1.41-2.24) and non-respiratory infections (OR 1.52 (95% CI:1.23-1.87) were associated with active PPI use. Infection associated mortality was also increased among active PPI users (OR 1.60 (95% CI:1.21-2.10). The results of this study show that use of PPIs is associated with an increased risk of severe community-acquired infections.

**Neoadjuvant Chemoimmunotherapy with Cisplatin, Gemcitabine plus GM-CSF in Locally Advanced Esophageal Cancer; a Phase II Study**

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IntroductionThe long-term survival for patients with locally advanced esophageal cancer remains unsatisfactory. Although several neoadjuvant chemotherapy regimens have been described, cisplatin-based chemotherapy appears to be the most effective in adenocarinoma and squamous cell carcinoma of the esophagus. This phase II study determines the toxicity, tumor response and survival in patients with locally advanced esophageal cancer receiving neoadjuvant treatment with cisplatin, gemcitabine and GM-CSF followed by surgery. Patients and MethodsThirty-eight patients with histologically proven esophageal adenocarcinoma (N=27) or squamous cell carcinoma (N=11), stages T2N1M0 through T3N1M1a, were treated with Gemcitabine (1250mg/m2; day 1 and 8) followed by Cisplatin (80mg/m2; day 1) and GM-CSF (300λg/day; day 9-19). Patients received a cycle every 3 weeks, up to a total of 6 cycles, after which the option of an esophagectomy was reviewed. Toxicity, tumor response and survival were analyzed. ResultsThirty-eight patients with a median age of 59,5 years were included in this phase II trial. Twenty-nine patients (76%) completed the total of 6 chemotherapy cycles, including one patient who received carboplatin instead of cisplatin during cycles two through six. Hematological toxicity was manageable with a grade 3 or 4 anemia, thrombocytopenia and leucocytopenia occurring in 21%, 55% and 18% of patients respectively. No treatment related deaths occurred. One patient (3%) was found to have a complete pathological response postoperatively. During chemotherapy, eighteen patients (47%) showed a clinical tumor response, 14 patients (37%) showed stable disease and 7 patients (18%) showed progression. In 31 patients the disease was found to be resectable and surgical esophagectomy with lymphadenectomy was undertaken. The median survival for patients with resectable disease was 33 months (95% confidence interval: 22-44) amid a 2 year survival rate of 54.8% (95% confidence interval: 37.3-72.4) with 6 patients alive at 72, 57, 44, 43, 43 and 38 months of follow-up.
Conclusion: Although the present study is a phase II series, the overall survival with cisplatin-gemcitabine plus GM-CSF seems favorable when compared to preoperative cisplatin-fluorouracil and chemoradiation in patients with advanced esophageal cancer, amid manageable toxicity. Larger randomized studies will be needed to validate our results.

## Survival in patients with Refractory Coeliac Disease and Enteropathy associated T cell Lymphoma

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Background: Coeliac disease may be regarded as refractory disease (RCD) when symptoms persist or recur despite strict adherence to a gluten free diet. RCD may be subdivided into types I and II with a phenotypically normal and aberrant intraepithelial T-cell population, respectively. RCD I seems to respond well to azathioprine/prednisone therapy. RCD II is usually resistant to any known therapy and transition into Enteropathy-Associated T-cell Lymphoma (EATL) is common. Aim: The aim of this study is to provide further insight into RCD and the development of EATL, by reporting on long term survival, risk of transition of RCD into EATL in one of the the largest cohorts of patients with complicated coeliac disease in a single center. Design and Methods: We have retrospectively compared four groups of patients with complicated coeliac disease: 43 RCD-I, 50 RCD II (total), of whom 26 RCD II who developed EATL after a period of refractoriness to a gluten free diet (secondary EATL) and 13 EATL patients without preceding history of complicated coeliac disease (de novo EATL). Every effort was made to ensure correct classification and accurate patient allocation.Results: No coeliac disease related mortality is recognized in the RCD I group. The overall five year survival in RCD I is 96%, in RCD II (total) is 58% (P=0.001) and in RCD II after developing EATL is only 8%. The 2 year survival in the de novo EATL is 20% versus 15% in secondary EATL (P=0.63).Twenty eight (56%) from 50 patients with RCD-II died, 23 (46%) due to EATL and 4 due to progressive refractory state with emaciation and one from neurocoeliac disease.
Conclusion: Remarkably, no patient with RCD I developed RCD II or EATL within mean follow up of five years (range 2-15 years). Fifty two percent of the RCD II patients developed EATL within 4-6 years after the diagnosis of RCD II. More aggressive therapy seems necessary in RCD II and EATL.

**The MYO9B gene is a strong risk factor for the development of refractory coeliac disease***

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Background & Aims: Coeliac disease (CD) is associated with HLA-DQ2 and HLA-DQ8 and has been linked to genetic variants in the MYO9B gene on chromosome 19. HLA-DQ2 homozygosity is associated with complications of CD such as refractory coeliac disease type II (RCD II) and enteropathy-associated T-cell lymphoma (EATL). We investigated whether MYO9B also predisposes to RCD II and EATL. Methods: Genotyping of MYO9B and molecular HLA-DQ2 typing was performed on 62 RCD II and EATL patients, 421 CD patients and 1624 controls. Results Three SNPs in MYO9B showed a significantly different allele distribution in RCD II and EATL patients compared to controls (p=0.00002, 0.05 and 0.04, respectively). The rs7259292 T allele was significantly more frequent in RCD II and EATL patients compared to CD patients (p=0.0003, OR 3.61 (95% CI 1.78-7.31)). The frequency of the haplotype carrying the T allele of this SNP was significantly increased in RCD II and EATL patients (11%), compared to controls (2%) and CD patients (3%) (OR 6.76 (95% CI 3.40–13.46), p=2.27E-09 and OR 4.22 (95% CI 1.95–9.11) p=0.0001, respectively). Both MYO9B rs7259292 and HLA-DQ2 homozygosity increase the risk for RCD II and EATL to a similar extent when compared to CD patients (OR 4.3 (95% CI 1.9–9.8) and 5.4 (95% CI 3.0–9.6), respectively) without evidence for interaction between these two risk factors.
Conclusion: This study shows that both MYO9B and HLA-DQ2 homozygosity might be involved in the prognosis of CD and the chances to develop RCD II and EATL.

**Marsh II enteropathy: identifying gluten sensitivity by gluten free diet and gluten challenge**

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Diagnosing coeliac disease in patients presenting with lymphocytic enteritis and crypt hyperplasia but without atrophy of the villi (Marsh II) is controversial. In this study we evaluated the clinical and histological effects of dietary interventions, i.e. gluten free diet (GFD) and gluten challenge, in patients who presented with symptoms suggestive of gluten sensitivity and Marsh II lesions in their small intestinal mucosal biopsies.Forty patients presented with symptoms of abdominal discomfort (63%), fatigue (49%), diarrhoea (20%), weight loss (10%), iron/folic acid deficiency (20/22%). HLA DQ2/8 markers were present in 77%, endomysial antibodies (EMA) in 38%, TG2 antibodies in 32%. Thirty-eight patients were motivated to start a gluten free diet, resulting in improvement of symptoms and improvement of histopathology to Marsh 0-I in all patients after 1 year. Two patients continued their normal diet and developed villous atrophy within two years and started a GFD. Twenty patients were motivated to subject to a gluten challenge (30 grams daily for 2 months). Twelve patients (60%) showed significant clinical and histological relapse (10/12 HLA DQ2/8+, 8/12 EMA+). In eight patients the challenge had no effect on clinical nor histological parameters (4/8 HLA DQ2/8+, 0/8 EMA+). Eighteen patients refused a gluten challenge because they experienced severe intolerance to gluten and were thus convinced of being gluten sensitive. We conclude that patients with Marsh II lesions should not automatically be diagnosed as coeliacs, although probably a majority truly is gluten sensitive. Dietary intervention studies (GFD and gluten challenge) may select those patients with severe clinical intolerance to gluten and gluten dependent enteropathy. Particularly these patients will profit from a GFD.

## Flowcytometry of intestinal T cells in Refractory Coeliac Disease

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Background: Refractory Coeliac Disease (RCD) is characterized by persisting mucosal pathology in spite of a strict gluten free diet. In RCD II a phenotypically aberrant (CD7+ CD3- CD4/8- cytoplasmic CD3+) Intraepithelial Lymphocyte (IEL) population is present, in contrast to RCD I. Since RCD II patients are at a much higher risk for development of Enteropathy Associated T-cell lymphoma (EATL), accurate discrimination between both types of RCD is of utmost importance. Aim: To evaluate flowcytometric analysis of small-bowel-biopsy derived lymphocytes to identify and quantify aberrant T cells in RCD patients as compared to coeliac disease patients on a glutenfree diet, and disease controls. We established reference ranges for various lymphocyte subsets as well as aberrant T-cells in the duodenal mucosa in several patient-groups.
Methods: T-cell immunophenotyping using a Fluorescence Activated Cell Scanner was performed on biopsy-derived lymphocytes, obtained by mechanical dissociation of fresh small bowel biopsies. The biopsies were obtained from 167 patients in our tertiary referral center for RCD, from 33 RCD, 8 EATL de novo, 17 active CD patients, 60 CD patients on a glutenfree diet and 49 controls without CD.
Results: Flowcytometry allowed objective, accurate and reproducible immunophenotypic evaluation of various lymphocyte subsets as well as aberrant IELs in RCD II, ranging from 20% to 90% of total IELs.
Conclusions: Flowcytometric analysis represents an accurate and reproducible way of evaluating the antigenic profile of several lymphocyte subsets in the small intestine. By discrimination of aberrant T cells it is well suited for the distinction between RCD I and II and the follow-up of RCD II patients. Moreover, these data can function as reference values for the assessment of several lymphocyte subsets in the small intestinal mucosa.

**Association of Runt-Related Transcription Factor 3 (RUNX3) and Organic Cation Transporters 1 and 2 (OCTN1/2) with Inflammatory Bowel Disease.**

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Introduction: RUNX3 is a member of the runt domain family of transcription factors. RUNX3 knockout mice develop a spontaneous colitis. RUNX3 resides on chromosome 1p36, a susceptibility locus for IBD. Polymorphisms in OCTN1, resulting in a disrupted binding site for RUNX are associated with Rheumatoid Arthritis. We looked for an association of RUNX3 and OCTN1/2 with IBD. RUNX3 and OCTN mRNA expression was assessed in inflamed and non-inflamed mucosa in patients and controls.
Methods: 543 patients (309CD/234UC) and 296 controls were included. 4 SNPs and 4 microsattelite markers were studied for RUNX3. For OCTN1/2 SNPs 207G→C, 1672C→G and 4 further SNPs, including the SNP disrupting the RUNX binding site rs3792876 were analyzed. Results were stratified for CARD15. RUNX3 and OCTN expression was determined by RT-QPCR ($\Delta\Delta$Ct) in mucosal tissue samples (14UC/16 CD/6 controls).
Results: *RUNX3:* SNP rs2236851 is associated with UC (OR 1.61 CI 1.11-2.32), pancolitis (OR 1.86 CI 1.08-3.21) and a borderline association with an early age of onset (OR 1.59 (CI 0.98-2.57)) and leftsided colitis (OR 1.86 (CI 0.99-3.51)) This was confirmed by TDT and haplotype sharing statistics. *OCTN1/2:* SNPs 207 G→C, 1672 C→G and rs3792876 were not associated with IBD, CD or UC. SNPs rs272893 and rs273900 were associated with CD (OR 2.16(1.21-3.59) and 2.40(1.43-4.05)) and subsets of CD. *Interaction of RUNX3, OCTN1/2 and CARD15 :* Binary logistic regression analysis shows an OR of 3.83(CI 1.26-11.67) for carriership of a risk-associated allele in RUNX3 and OCTN1/2 for UC versus CD. No epistasis with of CARD15 was found. *Mucosal expression:* RUNX3 mRNA expression is increased ($p<0.05$) and OCTN is decreased ($p<0.05$) in inflamed colonic mucosa, but not in ileal mucosa in CD and UC compared to non-inflamed and controls.
Conclusions: We provide evidence for the genetic association of RUNX3 with UC and confirmed the association for CD with OCTN1/2, although this involves other SNPs than previously described. We showed an increased risk for UC in patients carrying both the RUNX3 and OCTN risk-associated alleles. RUNX3 mRNA is upregulated and OCTN mRNA downregulated in inflamed colonic mucosa compared to non-inflamed mucosa of patients or controls. Impaired activation of RUNX3 might result in decreased activity of the TGF-ß pathway, an important downregulator of mucosal inflammation. Functional studies concerning RUNX3 mutations are needed to clarify the role of RUNX3 in UC susceptibility.

**A large, nationwide, case-control study for the association of DLG5, OCTN1/2 and CARD15 with Inflammatory Bowel Diseases in the Netherlands.**

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Introduction: Chronic inflammatory bowel diseases (IBD) (Crohn's disease(CD) and ulcerative colitis(UC)) have a complex genetic background. Conflicting results have been reported in association studies for genetic variants in Drosophila Discs Large Homologue 5 (DLG5) and in organic cation transporters 1 and 2 (OCTN1/2) and IBD. Therefore, a large, collaborative, nationwide study was conducted. Methods: 3061 mainly Dutch Caucasian IBD patients (1818 CD/1243 UC) and 1518 healthy controls were included. Phenotypic details were available for 2317 patients (1497 CD/820 UC). For DLG5 the risk associated SNP 113G→A and rs2165047 and for OCTN1/2 SNPs 1672 C→T and -207G→C were analyzed. Additional SNPs (rs272893, rs273900, rs274551) in OCTN1/2 were analyzed in a subset of 1263(695 CD/568 UC) patients. Results were stratified for the risk associated alleles for CARD15. Results: For DLG5, 113G→A was associated with IBD (p=0.022), UC (p=0.033) and proctitis in UC (p=0.017) but not with CD. rs2165046 was associated with IBD (p=0.0042) CD (0.0043), familial occurrence in CD (p=0.0050) and proctitis in UC patients (p=0.033). OCTN1/2 SNPs 1672C→T and -207G→C were not associated with IBD, CD or UC except for subsets of stricturing CD (1672C→T, p=0.046) and leftsided UC or colectomy in UC (-207G→C, p=0.02 and p=0.035). rs272893, rs273900, rs274551 in OCTN1/2 were significantly associated ($p<0.05$) with an increased risk for IBD and CD. rs274551 was associated with UC(p=0.026), particularly with an early age of onset (p=0.008). No interaction with CARD15 was found for either DLG5 or OCTN1/2. Conclusion: In this large, well phenotyped, nationwide study in the Netherlands, we found an association of DLG5 113G→A with IBD, though not with CD but with UC.

Furthermore rs2165046 (haplotype B) in DLG5 was associated with IBD and CD. We did not find an association for OCTN1/2 with IBD, CD or UC and SNPs 1672C→T and -207G→C, except for stricturing CD and leftsided UC or need for colectomy in UC. However, significant association was found with IBD, CD and (early onset) UC, for three additional SNPs in OCTN1/2. This supports the view that OCTN1/2 might be the associated gene in the IBD5 locus, but further analysis concerning the haplotype structure of IBD5 is needed. No epistasis between DLG5, OCTN1/2 and CARD15 was observed. Large, nationwide, case-control studies in rigorously phenotyped cohorts of IBD patients are needed to confirm previously described genetic associations.

**Bile acid stimulated expression of the Farnsesoid X Receptor enhances the immune response in Barrett Esophagus**

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Barrett esophagus (BE) is a Th2 mediated chronic inflammatory condition resulting in an increased risk of the development of esophageal adenocarcinoma. Exposure to acid and bile containing reflux is thought to play an important role in the induction and maintenance of BE. The exact mechanism whereby bile acids induce these inflammatory processes is largely unknown. The Farnesoid X Receptor (FXR) is a nuclear receptor involved in the regulation of both synthesis, transport, and absorption of bile acids. FXR activation also results in the induction of the innate immune response. We aimed to investigate the relationship between DCA and FXR and the induction of one the target genes IBABP, as well as two key chemokines, IL-8 and MIP3$\alpha$.In vivo expression levels of FXR, IBABP, IL-8, and MIP3$\alpha$ were determined by semi-quantitative RT-PCR in biopsy specimens taken from Barrett's epithelium and squamous epithelium of 15 patients with BE. FXR protein expression was determined by immunohistochemistry. The effect of exposure to deoxycholicacid (DCA) on transcription and translation levels of FXR, IBABP, IL-8 and MIP3$\alpha$ in the esophageal adenocarcinoma cell line TE7, in either the absence or presence of the FXR inhibitor guggulsterone were investigated by RT-PCR.FXR expression was found in biopsy specimens of patients with BE on both the RNA and protein level. A 2.3-fold (p=0.02) increase in FXR mRNA was found in Barrett's epithelium compared to squamous epithelium of the same patient. IBABP showed a 2.2-fold increase (p=0.003). Similarly, a 1.5-fold increase (p=0.04) in IL-8 expression, and a 1.7-fold increase (p=0.02) in MIP3$\alpha$ expression was found in biopsies from Barrett's epithelium. Exposure of TE7 cells to DCA, resulted in an induction of FXR (4.7-fold; p=0.002), IBABP (1.9-fold;p=0.02), IL-8 (3.3-fold;p=0.01) and MIP3$\alpha$ (19.2-fold;p=0.000). This increase in FXR levels was not observed if cells were pre-treated with guggulsterone (p=0.001). Pretreatment with guggulsterone also significantly reduced IBABP, IL-8, and MIP3$\alpha$ expression levels (resp. 1.4-fold;p=0.15, 2.9-fold;p=0.05, and 3.0-fold;p=0.002).
Conclusions: The bile acid receptor FXR and its target gene IBABP, as well as the chemokines IL-8 and MIP3$\alpha$, are increased in Barrett's epithelium compared to squamous epithelium of BE patients. The in vivo induction of FXR by DCA suggests that bile acids may actively induce the inflammatory response in BE by recruiting cells that are involved in this process.

**Behavioral therapy for treatment of childhood constipation: A randomized controlled trial**

*MLDS project no. SWO 02-16*

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Context: It is suggested that the addition of behavioral components to laxative therapy improves continence in children with functional fecal incontinence associated with constipation.

Objective: To evaluate clinical effectiveness of behavioral therapy in addition to conventional treatment.

Design and setting: Randomized controlled trial conducted from November 2002 to August 2004 at a university based gastrointestinal outpatient referral center in the Netherlands.

Patients: 129 children aged 4-18 years with functional constipation as defined by the classic Iowa criteria.

Interventions: Patients were randomly assigned to 22 weeks (12 visits) of either behavioral therapy (BT) or conventional treatment (CT). BT incorporated two age modules (4-8 years, ≥8 years).

Main Outcomes Measures: Defecation frequency (DF), fecal incontinence frequency (FIF), success rate, relapse, stool-withholding behavior (SWB) and general behavioral problems (CBCL). Success was defined as DF≥3/wk and FIF≤0.5/wk irrespectively of laxative use.

Results: Consistent with an intent-to-treat approach, random regression analyses revealed no significant difference between CT and BT on success rate (p=.179) with 62.9% (95% CI=[50.0-74.2%]) in CT and 57.2% (95% CI=[43.7-69.7%]) in BT at posttreatment and a success proportion of 65.6% (95% CI=[52.2-76.9%]) in CT and 53.6% (95% CI=[40.3-66.5%]) in BT at 6-months follow-up. DF showed a treatment-by-time interaction (p=.025) with children in CT increasing DF posttreatment significantly more, but at follow-up this effect disappeared. There were no differences between treatments found for FIF and SWB. For the proportion of children with severe behavioral problems (CBCL T-score>63) a treatment-by-time interaction emerged with less children with behavioral problems in BT (p=.025). Large differences were observed between CT and BT at follow-up (32.1% vs. 12.8%; p=.017). An age-by-treatment interaction (p=.035) showed this difference was particularly caused by younger children in BT (younger: 15.7%, older: 37.8%).

Conclusions: BT was equally successful as CT in treating childhood constipation and stool-withholding behavior. For younger children with constipation and severe behavioral problems, BT proved to be more beneficial.

**MYH-based strategy towards identification of novel genes somatically mutated during intestinal tumor progression**
*MLDS project no. MWO 04-21*

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Bi-allelic germline mutations in the *MYH* gene, a key element of the base excision repair (BER) reaction, predispose the individual to the development of multiple adenomatous polyps in the colon-rectum. Loss of *MYH* function results in G:C->T:A somatic mutations in the adenomatous polyposis coli (*APC*) gene, but it is likely that additional mutations in genes other than *APC* can play a rate-limiting roles in intestinal tumorigenesis. Taking advantage of this feature of BER, *Myh* knock-out mice (*Myh*-/-), were bred with the $Apc^{+/1638N}$ model for intestinal tumorigenesis to identify novel genes somatically altered during intestinal tumor initiation and progression.
Compound $Apc^{+/1638N}/Myh^{-/-}$ mice showed an increase in gastrointestinal tumor multiplicity when compared with $Apc^{+/1638N}/Myh^{+/+}$, though no differences were found in progression towards malignancy. A proportion of the intestinal tumors derived from compound mutant mice were found to carry somatic G:C->T:A transversion at the wild type *Apc* allele. *K-Ras* and *β-catenin* mutation analysis in combination with β-catenin IHC analysis did not reveal any difference between $Apc^{+/1638N}/Myh^{-/-}$ and $Apc^{+/1638N}/Myh^{+/+}$ polyps.
We are currently conducting expression profiling analysis of the $Apc^{+/1638N}/Myh^{-/-}$ and $Apc^{+/1638N}/Myh^{+/+}$ tumors to identify a subset of differentially expressed candidate genes that might represent specific BER targets in the intestine. These genes will subsequently be investigated by somatic mutation analysis in mouse and human *Myh*-mutant tumors.

**The Sab adhesins of Helicobacter pylori: acid-responsive regulation of expression and their role in the modulation of the host immune response**

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The human gastric pathogen Helicobacter pylori is the major cause of gastritis and peptic ulcer disease and is also associated with the development of gastric cancer. One factor allowing colonization by H. pylori is adhesion to the gastric epithelium via specific adhesins. Expression of several H. pylori adhesins is subject to phase variation (which randomly determines the "on"/"off" status of a gene), and may also be acid-responsive. Two of the important adhesins are SabA/SabB. Our aim was to study the regulation of expression and role in infection of the Sab adhesins of H. pylori.H. pylori strains G27 and 26695 were grown for six hours in medium with the acidity adjusted to pH 7.0 or 5.5. Regulation of transcription was assessed using Northern hybridization. The phase variation status of sabA and sabB was assessed by nucleotide sequencing of the coding regions. Gerbils were infected with H. pylori strain 7.13 and the isogenic sabA and sabB mutants. The gerbils were sacrificed 12 weeks after administration of H. pylori and the severeness of inflammation was assessed in the gastric mucosa. Transcription of the sabA and sabB genes decreased when H. pylori strains G27 and 26695 were grown in acidic conditions (pH 5.5) compared to pH 7.0. This was independent of the "on"/"off" status of the genes (G27: sabA "on", sabB "on" vs 26695: sabA "off", sabB "off"). The gerbils colonized with the sabB mutant showed a significant increased level of acute inflammation (P=0.040), surface degeneration (P=0.025) and dysplasia (P=0.040) when compared to the wild-type strain. Neither SabA nor SabB was required for colonization by H. pylori of the gerbil gastric mucosa.Acid-responsive modulation of adhesin expression may allow H. pylori to regulate its adhesion properties, which would enable the bacterium to escape unfavorable environmental conditions. Regulation of Sab transcription seems independent of phase variation, and this may allow regulation of adhesin expression at both the cellular and the population level. Finally, absence of SabB expression results in increased inflammation, suggesting that SabB has immunosuppressive activity.
Concerted modulation of bacterial gene expression and host immune response are likely to contribute to the chronicity of H. pylori infection.

**Oral administration of alkaline phosphatase ameliorates colitis**

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Background & Aims: Crohn's disease (CD) and ulcerative colitis (UC) are chronic multifactorial inflammatory bowel diseases with unknown etiology, but a dysregulated mucosal immune response to gut-derived bacterial antigens is thought to be involved. Toll-like receptor ligands, especially lipopolysaccharide (LPS), seem to contribute in the maintenance of the disease. Previously, we showed that the enzyme alkaline phosphatase (AP) is able to detoxify LPS and the aim of this study was therefore to examine its role in inflammatory bowel diseases.Methods: We examined intestinal AP (iAP) mRNA expression and LPS-dephosphorylation in intestinal biopsies of control persons and IBD patients, and we studied the effect of orally administered iAP-tablets on the progression of dextran sodium sulphate-induced colitis in rats.Results: In healthy persons, iAP mRNA and protein expression was high in the ileum relative to the colon. iAP mRNA expression was not altered in CD patients, but it was markedly reduced in UC patients when inflamed tissue was compared to non-inflamed tissue. Oral administration of iAP-tablets to colitic rats resulted in a significant attenuation of colonic inflammation as reflected by reduced mRNA levels for TNF$\alpha$, IL-10, IL-6 and iNOS, a reduced iNOS-staining and inflammatory cell influx, and a significantly improved morphology of the intestinal wall.
Conclusion: The present study shows that epithelial iAP mRNA expression is reduced in UC patients. The rat model indicates that oral administration of iAP can replenish the intestinal tract with active AP-enzymes, resulting in a significant reduction of inflammation. This may provide new opportunities for the treatment of IBD. This work was financially supported by the Dutch organisation for Scientific Research (NWO).

**The specific nicotinic α7 receptor agonist AR-R17779 reduces inflammation in a mouse model of DSS colitis**

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The parasympathetic nervous system represses inflammation through the nicotinic α7 acetylcholine receptor (α7 nAChR) which is expressed on macrophages. As macrophage activation by luminal antigens is an important feature in de induction and perpetuation of inflammatory bowel disease, the α7 nAChR might be an important therapeutic target to reduce gastrointestinal inflammation. Therefore we assessed the potency of a selective α7 nAChR agonist AR-R17779 to ameliorate gastrointestinal inflammation in a DSS colitis mouse model. Mice received 1.5% DSS in drinking water for up to 7 days. Vehicle (0.9% NaCl), 1 mg/kg or 5 mg/kg AR-R17779 was administered daily by intraperitoneal injection. The mice were killed after 7 days and colonic inflammation was assessed according to clinical parameters. To determine bacterial translocation, caudal lymph nodes were homogenized and plated onto blood agar plates. After 24h incubation at 37oC, the amount of colony forming units per lymph node was assessed. The data represent the mean ± SE. Differences between groups were analysed using the nonparametric Mann-Whitney U test. Treatment with AR-R17779 significantly reduced DSS-induced weight loss, colonic shortening, histopathology score and disease activity index (table 1). Also, bacterial translocation (number of colony forming units cultured from caudal lymph node after 7 days of DSS) was significantly decreased after treatment with AR-R17779 [vehicle: 409.0±168.0, AR-R17779 1 mg/kg:106.0±60.0, AR-R17779 5 mg/kg: 4.0±2.0 ($p<0.05$)]. Administration of AR-R17779 significantly ameliorates disease parameters in DSS colitis. In addition, treatment with AR-R17779 reduced bacterial translocation indicating that intestinal barrier function is improved. These data suggest that α7 nAChR-agonists might be a potential new treatment for inflammatory bowel disease.

**Differential transcriptional responses of intestinal mucosa upon intake of log-phase, stationary and dead cells of Lactobacillus plantarum WCFS1 in vivo in humans**

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The human gut mucosa respons to commensal and probiotic species in the gut lumen is not clear. We investigated the effects of different preparations of L.plantarum WCFS1, a strain originally isolated from human saliva, on gene expression in duodenum mucosa. Eight healthy volunteers participated in a randomized double-blind cross-over study with four interventions. Volunteers were instructed to drink 100-ml beverages at 30-min intervals during 6 h. The beverages contained, in total, 1% glucose and 8% maltodextrin (glucmalt; placebo), 1012 viable L. plantarum WCFS1 cells harvested during the stationnary phase of growth, 1012 L. plantarum WCFS1 heat-killed cells of the same preparation, or 1012 L. plantarum WCFS1 cells harvested from the logarithmic growth phase, all in glucmalt. Subsequently, duodenum tissue samples were obtained by flexible gastroduodenoscopy. Gene expression profiles in the tissue samples were determined using Affymetrix U133 set microarray chips, and analysed applying a Gaussian linear regression model. Only probe sets that were significantly regulated compared to placebo were considered for further analysis. A fold change? 10% was considered as a differenttially expressed probe set. Ingenuity pathway analysis and subsequent literature exploration using Genbank's GeneRIFs and the iHOPS database was used to extrapolate the gene results to biological processes. Intake of stationary, heat-killed and log-phase L. plantarum WCFS1 mediated the expression of 277 (245 up, 32 down), 281 (128 up, 152 down) and 296 (275 up, 21 down) probe sets, respectively. At the pathway level, stationary L.plantarum WCFS1 mainly affected cell-cell signalling and immune responses. Especially genes that are associated with NF-kB activation and apoptosis were mediated. Log-phase L. plantarum WCFS1 induced an upregulation of oxidative phosphorylation, whereas both stationary phase and heat-killed L. plantarum WCFS1 induced a downregulation of this process. Log-phase L. plantarum WCFS1 also induced protein ubiquitination and antigen presentation pathway, suggesting that these cells induced protein turnover and immune responses. Heat-killed L. plantarum WCFS1 induced minor effects. Hematological system development and -function and integrin signalling, which are involved in immune responses and cell death, were mediated.
In conclusion, oral intake of different preparations of L. plantarum WCFS1 triggered specific responses on the transcriptional level in gut mucosa

**Gastric *Helicobacter* species colonizing strict carnivores express two different, functional urease enzymes**

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The nickel-dependent enzyme urease is an essential virulence factor of *Helicobacter* species colonizing the gastric environment. Concerted expression of virulence factors is often a requirement for colonization by bacterial pathogens. In *H. pylori*, urease expression is induced by the NikR regulatory protein in response to availability of the nickel cofactor. Nickel is scarce in the mammal host, and is mostly acquired via vegetarian dietary sources. This is a potential problem for gastric *Helicobacter* species colonising the nickel-limited gastric environment of strict carnivores. Recently, a putative second urease gene cluster (*ureA2B2*) was detected in three gastric *Helicobacter* species colonizing carnivores. This gene cluster was not detected in other *Helicobacter* species. The aim of this study was to characterize the transcriptional regulation and contribution to urease activity of both urease systems using *H. mustelae* as model organism.
To study expression of both urease homologs *H. mustelae* NCTC 12198 and its isogenic *nikR* mutant were cultured under nickel-restricted and nickel-supplemented conditions. Regulation of *ureB* and *ureB2* transcription was assessed by Northern hybridization and immunoblotting. UreA2B2 and UreAB urease activity was measured in *nikR*/*ureB* and *nikR*/*ureB2* double mutants. A *nikR*/*ureB*/*ureB2* triple mutant was used as negative control.
Both urease homologs of *H. mustelae* were expressed in nickel-restricted conditions, but were conversely regulated upon nickel-supplementation. Addition of nickel to a final concentration of 100 nM resulted in complete transcriptional repression of UreA2B2, whereas UreAB expression was induced. Insertional mutagenesis of *nikR* resulted in constitutive expression of both urease homologs, independent of the nickel concentration in the medium. Maximum activity of UreA2B2 in *H. mustelae* was ~0.5 U, whereas UreAB activity could reach up to 20 U of activity in nickel-supplemented conditions.
Three carnivore-colonizing *Helicobacter* species express a second urease system, which is only active at severe nickel-restriction. This second urease system seems absent from *Helicobacter* species colonizing omnivores and herbivores. The expression of UreA2B2 is possibly an adaptation of carnivore-colonising *Helicobacter* species to the limitations of the diet of their carnivorous host, by using a urea-degrading enzyme with biochemical properties well suited for low nickel availability.

## *Gpx2* and *Aqp8* as new markers for colonic inflammation in experimental colitis and IBD: an important role for $H_2O_2$?

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Different mouse models of inflammatory bowel diseases (IBD) demonstrate various aspects of the pathophysiology of IBD. We looked for overlapping gene expression profiles in three different mouse models of experimental colitis in order to find new genes that could be used as general markers in IBD and future therapeutic targets.
Using Agilent mouse TOX oligonucleotide microarrays, we analyzed the gene expression profiles in three widely used models of experimental colitis: TNBS, DSS and $CD4^+CD45RB^{high}$ transfer and looked for overlapping gene expression in these models. Overlapping genes were analyzed using Lightcycler in biopsy material from human IBD and control tissue.
Compared to control mice, in DSS, TNBS and the CD45RB transfer colitis mice five known genes: *Expi*, *Gpx2*, *Mcpt1*, *Retnlb* and *Sulf2* and two unknown genes were up regulated in all three models and two genes: *Aqp8* and *Klk5* were down regulated. In human CD and CU biopsies one of the up regulated (*Gpx2*) and one of the down regulated (*Aqp8*) genes in the mouse models were also differentially expressed in affected colonic tissue of patients with IBD.
Since both *Gpx2* (glutathione peroxidase 2) and *Aqp8* (aquaporin 8) are involved in $H_2O_2$ metabolism (*Gpx2* as a radical scavenger while *Aqp8* facilitates its diffusion (Bienert et al, JBC 2006) up regulation of *Gpx2* and down regulation of *Aqp8* could be a mechanism to defend against severe oxidative stress and indicate that $H_2O_2$ is an important mediator in the inflammatory process in the colon.
In conclusion, *Gpx2* and *Aqp8* are markers for inflammation in the colon and are potentially new targets for future therapy.

**Withdrawal flares after treatment with peginterferon alpha-2b alone or in combination with lamivudine in HBeAg-positive chronic hepatitis B**

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Hepatitis flares can occur after withdrawal of antiviral therapy (withdrawal flare) and have been associated with liver failure. Aim: To investigate the frequency and severity of flares after discontinuation of PEG-IFN $\alpha$-2b or its combination with lamivudine in HBeAg positive chronic hepatitis B. Methods: A total of 266 patients participating in a global randomized controlled study were assigned to 52 weeks of PEG-IFN $\alpha$-2b alone (100$\lambda$g 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. Withdrawal flares were defined as post-treatment ALT of more than 3x ALT at week 52 and more than 5x upper limit of normal (ULN). Results: Withdrawal flares occurred in 26% of patients treated with PEG-IFN and lamivudine, and 22% of patients treated with PEG-IFN alone (p=0.21). Mean maximum ALT for withdrawal flares after combination therapy was 13.5 x upper limit of normal (ULN) compared to 9.9 x ULN after PEG-IFN alone (p=0.14). In multivariate analysis, patients with HBV genotype B (OR 34.8, 95% CI 3.0 - 406.7), C (OR 25.0, 95% CI 2.7 - 232.5) or D (OR 16.2, 95% CI 2.0 - 133.2) had a significantly higher risk for withdrawal flares after PEG-IFN monotherapy compared to patients with genotype A. Furthermore, high HBV DNA at week 52 was predictive for withdrawal flares in PEG-IFN treated patients (OR 1.3 for each 1log10 HBV DNA increase, 95% CI 1.0 - 1.7). Absence of HBeAg sero-conversion was the only independent predictor of withdrawal flares in the combination therapy group (OR 5.5, 95% CI 1.4 - 21.9). The occurrence of withdrawal flares tended to decrease HBeAg loss post-treatment in the combination therapy group (4% vs. 22%, p=0.08) and HBeAg relapse occurred significantly more often in these patients (85% vs. 25%, p<0.001), while this was not observed for PEG-IFN monotherapy. Conclusion: Withdrawal flares occurred equally after discontinuation of PEG-IFN $\alpha$-2b or its combination with lamivudine, but tended to be more severe after combination therapy. The strongest predictor of withdrawal flares after PEG-IFN $\alpha$-2b monotherapy was non-genotype-A infection, while for combination therapy this was the absence of HBeAg-seroconversion at week 52. Since withdrawal flares do generally not result in HBeAg loss, close monitoring of patients at increased risk for developing withdrawal flares and rapid re-initiation of antiviral therapy is recommended.

## High prevalence of hepatitis C in the general Dutch population

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Chronic hepatitis C virus (HCV) is often an asymptomatic disorder that can be transmitted by blood-blood contact. This is reflected by a relatively high HCV prevalence in at-risk groups. For example, the prevalence in Dutch haemophilia patients is 54% while it is higher (up to 74%) in intravenous drug users. In contrast, the prevalence in screened blood donors appears to be very low (0.008%). However, the actual prevalence in the population at large is unknown, hence the need for population-based serologic studies. These data are desirable because it allows medical professionals and policymakers to develop and evaluate efforts with respect to treatment and prevention. The objective of this study is to estimate the prevalence of hepatitis C in a general population sample living in an urbanised region in the Netherlands. We randomly selected 1231 EDTA blood samples that were submitted for analysis of biochemical parameters to a servicing laboratory (SHO). SHO provides laboratory facilities to general practitioners in region Arnhem/Nijmegen. HCV antibody testing was performed using a three-step approach. For initial screening, an enzyme immunoassay (bioelisa HCV 4.0, Biokit, Spain) was used. The cut-off value was determined according to the manufacturers instructions by multiplying the optical density (OD) value by 0,9. Ratios of sample OD values and cut-off values of > 1 was considered positive. Positive samples were subjected by a second, microparticle enzyme linked immunoassay (AxSYM HCV version3.0, Abbott laboratories, IL, USA). Positive results were further confirmed using a Western blot assay. All assays were performed according to the manufacturers instructions.A total of 10 patients (0.81%) tested positive for HCV antibodies. The group consisted of 7 females and 3 males with a mean age of 63.3 yrs (range 25-80 yrs). Average OD/cut-off ratio of the screening assay was 2.9 (range 1.0-7.3) and serological findings were confirmed in all. From our results we conclude that the HCV prevalence in the general Dutch population is considerably higher than anticipated. This implicates that the reservoir for HCV in The Netherlands is sizeable which has important implications for the chances of transmission of the disease.

**Limited role for routine ascitic culture as a diagnostic tool for spontaneous bacterial peritonitis in the era of prophylactic antibiotics**

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Spontaneous bacterial peritonitis (SBP) is a severe and common complication in patients with cirrhosis and ascites, with a reported incidence of 10-30% in hospitalized patients. Diagnosis of SBP is established when polymorphonuclear count (PMN) exceeds 0.25 x $10^9$/l. A bedside culture of ascitic fluid in blood-culture bottles is routinely performed to optimize treatment. Most of the data concerning the incidence and characteristics of SBP date from the era when a smaller percentage of patients used prophylactic antibiotics. We therefore analyzed results obtained in diagnosing SBP in our center and compared this to literature.Data of all ascitic fluid cultures performed in cirrhotic patients between January 2003 – December 2005 on the ward of gastroenterology and hepatology were analyzed. Retrospective chart analysis was carried out for corresponding patients. Follow up was until May 1, 2006. Kaplan-Meier was used for survival analysis. In total 356 ascites cultures were performed in 129 patients. SBP was detected in 56 (15.6%) of the samples. In only 22/56 (39.4%) a causative micro-organism was found. The most common isolated bacteria was E. Coli, 9/22 (40.9%), followed by coagulase-negative staphylococci, 3/22 (13.6%), and C. Albicans, 3/22 (13.6%). 11/22 (50%) of the culture-positive SBP was under prophylactic antibiotics, while prophylaxis in the culture-negative group was used in 25/34 (74.5%) samples (p=0.07). With regard to the characteristics of ascitic fluid a significant relation between an ascitic fluid protein count <10 g/l and a high PMN-count (p= 0.03) was seen, with no difference between culture-positive and culture-negative samples, mean 4.43 g/l vs 4.26 g/l (p=0.95). Overall 1-year mortality in the SBP population was 52% with a mean survival of 69.3 days. There was no significant difference in survival between culture-positive and culture-negative SBP (p=0.15). Conclusions: The in-hospital incidence of SBP is low compared to literature. This can well be attributed to the more extensive use of quinolone-prophylaxis in patients with cirrhosis and ascites in recent years. The apparent low cost-effectiveness of the ascitic cultures together with the poor overall survival in both culture-positive and culture-negative SBP makes the standard inoculation of ascitic fluid in blood-culture bottles debatable.

**In Primary Sclerosing Cholangitis the long-term risk for colorectal cancer is more than twofold higher than the risk for cholangiocarcinoma. Results of a long-term cohort study**

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Although it has been well established that patients with primary sclerosing cholangitis (PSC) carry a high life time risk for cholangiocarcinoma (CCA) and colorectal cancer (CRC), relatively few long-term studies have quantified these risks. The aim of this study was to determine the actuarial incidence of malignancies in a cohort of PSC patients followed for up to 25 years. We analyzed all patients who were diagnosed with PSC between 1980- 2006 in two university medical centres in the Netherlands. Relevant data were retrieved from medical charts. The cumulative risk of cancer and survival was calculated with the actuarial method (Kaplan-Meier). A total of 211 patients were included of which 143 (67.8%) patients were male. The median age at diagnosis was 35 years (range 11-75). Altogether 126 (59.7%) patients had concurrent IBD (ulcerative colitis, n=93; Crohn's disease, n=23; indeterminate colitis, n=10).Patients were followed for a mean period of 9.6 years. Estimated median transplantation-free survival was 14 years. During follow-up 45 (21.3%) patients died and in 42% this was cancer related. Thirty-nine patients developed malignancies of which 15 (7.1%) were CCA. In five cases CCA was diagnosed within one year of diagnosing PSC. The estimated risk of CCA after 10/20 years was 8.6/8.6%. No significant difference in CCA-incidence between patients with or without concurrent IBD was found. Sixteen (7.6%) patients developed CRC. The overall estimated risk of CRC after 10/20 years was 9.0/19.3%. In patients with concurrent IBD the 10/20 years risk for CRC was 13.2/26.4% and without IBD 2.3/2.3% (p=0.0126 log-rank test). The 10/20 years risk of CRC or CCA was 15.2/26.7%. Other malignancies diagnosed during follow-up included gallbladder carcinoma in two patients, pancreatic cancer in one, lymphomas in three and melanoma and gastric cancer in one case each. Conclusion: Patients with PSC have a highly increased risk of developing cancer, in particular IBD-associated CRC.

**Cysts of PRKCSH mutated polycystic liver disease patients lack hepatocystin but over-express MUC1**

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Polycystic liver disease (PCLD) is an autosomal dominant inherited condition characterized by numerous cysts scattered throughout the liver. PCLD is caused by mutations in *PRKCSH* or *SEC63*, encoding hepatocystin and SEC63p respectively. It is unknown how hepatocystin and SEC63p cause a neocystogenic disorder. MUC1 is a glycoprotein expressed at the apical surface of ductal epithelia of a great variety of tissues and is involved in cell-cell interactions, signaling, and metastasis. We speculated that germline *PRKCSH* mutations are associated with a loss of hepatocystin and similarly with a deregulation of MUC1 in cyst epithelia.
We stained cyst tissue samples obtained by laparoscopic fenestration (n=10) and normal liver tissue samples (n=3) with antibodies directed against hepatocystin, SEC63p, MUC1, CK18 and CK19. Five patients had a *PRKCSH* mutation and one patient a *SEC63* mutation, while the remaining 4 patients were wild type for both genes.
Hepatocystin was expressed in hepatocytes and bile ducts, and in cyst epithelium of *PRKCSH* mutation negative patients. By contrast the majority of cysts (90%) in *PRKCSH* mutation carriers was negative for hepatocystin and displayed a cytoplasmic MUC1 staining. On the contrary, cysts that did stain hepatocystin were negative for MUC1. Bile ducts and cyst epithelium from wild type patients had a physiological staining for MUC1. The presence of bile duct origin was confirmed by CK18 and CK19 staining pattern. SEC63p was present in all cyst epithelium, hepatocytes and bile ducts regardless of mutation status.
In conclusion: The majority of cysts of germline *PRKCSH* mutation carriers do not stain hepatocystin, suggesting a double hit phenomenon. In addition, these cysts are MUC1 positive implicating a role for MUC1 in the cystogenesis of the disease.

**Biliary drainage attenuates post-ischemic reperfusion injury in the cholestatic rat liver**

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Oxidative stress has been identified as a pathogenic feature of parenchymal injury in cholestasis. During major liver resections, vascular inflow occlusion can be applied to reduce intraoperative blood loss. The combination of ischemia and oxidative stress potentially enhances post-ischemic reperfusion injury. Biliary decompression relieves oxidative stress in cholestasis. Therefore, preoperative biliary drainage seems a worthwhile intervention in patients undergoing major liver resection, although this is debatable in distal tumors which are resected without partial liver resection. The aim of this study was to assess the effect of biliary decompression on hepatic ischemia and reperfusion (I/R) injury in a bile duct ligation (BDL) model in the rat. Male Wistar rats were randomized into three groups: The first group (n=12) underwent 30 minutes partial liver ischemia after 7 days BDL. The second group (n=12) underwent internal drainage (ID) after 7 days BDL and following 5 days, was subjected to ischemia. Control animals (n=12) underwent two sham laparotomies at 7 and 12 days, respectively, and subsequent ischemia. The rats were sacrificed after 24h of reperfusion. The following outcome parameters were assessed: plasma AST and ALT, hepatic oedema, lipid peroxidation, histopathology, hepatic synthetic function, inflammatory response, hepatic myeloperoxidase (MPO) activity and the total antioxidant activity of the liver.Serum levels of AST and ALT were significantly higher after 30 minutes, 6 hour and 24 hour of reperfusion as compared to the control and ID group ($p<0.05$). Prothrombin time, plasma IL-6, IL-10, GRO/KC, MPO, necrosis, lipid peroxidation and hepatic oedema were all significantly increased in the BDL group after 24h reperfusion ($p<0.05$ for control and ID). Moreover, the antioxidant activity was strongly decreased in the cholestatic group ($p<0.01$ for control and ID). No significant differences for most parameters were seen in the ID group as compared to the control group.
Conclusion: The cholestatic rat liver is more susceptible to post-ischemic reperfusion injury, probably mediated by decreased antioxidant activity and an increased inflamematory response. These injurious effects were attenuated by biliary decompression. The results of this study suggest an increased risk of inflammatory events, such as clamping of the portal triad during liver resection, in the presence of cholestasis.

**Non-anastomotic biliary strictures after liver transplantation: novel insights in presentation and pathogenesis**

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Background: Non-anastomotic biliary strictures (NAS) are a serious complication after orthotopic liver transplantation (OLT). The exact pathogenesis is unclear. However, previous studies have strongly suggested two major groups of risk factors: a) preservation injury (ischemia / reperfusion) -related factors and b) variables related to immunological processes. The time of presentation, severity and anatomical localization of NAS after OLT varies widely among different patients. Aim: To identify risk factors for, and performed a comprehensive analysis of the anatomical localization and the severity of NAS at the time of initial presentation in a large group of liver transplant recipients with long-term follow-up. Methods: A total of 487 adult liver transplants performed between 1986 and 2003 were studied. All imaging studies of the biliary tree were reviewed. Localization of NAS at first presentation was categorized into 4 anatomical zones of the biliary tree. Severity of NAS was semi-quantified as mild, moderate or severe. A large number of donor, recipient and surgical variables were analyzed to identify risk factors for NAS. Results: NAS developed in 81 (16.6%) of the livers. Thirty-seven (7.3%) were graded as moderate to severe. In 85% of the cases, anatomical localization of NAS was around or below the bifurcation of the common bile duct. A large variation was observed in the time interval between OLT and first presentation of NAS (median 4.1 months; range 0.3-155 months). NAS presenting early (≤ 1 year) after OLT was strongly associated with preservation-related risk factors and most frequently located in the central bile ducts. NAS presenting late (> 1 year) after OLT was found more frequently in the periphery of the liver and associated with immunological risk factors. Discussion: By separating cases of NAS based on the time of presentation after transplantation, we identified significant differences in risk factors, indicating different pathogenic mechanisms depending on the time of initial presentation. Early NAS is strongly correlated with ischemia related risk factors, whereas Late NAS is more associated with immunologically related risk factors. These finding have important implications for the development of new strategies to prevent or treat NAS.

## $^{99m}$TC-GSA scintigraphy with SPECT in the assessment of hepatic function and functional volume during liver regeneration in a rat model

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Small animal models are crucial in order to gain insights in the complex recovery mechanisms of liver function during liver regeneration. $^{99m}$Tc-mebrofenin hepatobiliairy scintigraphy (HBS) has been introduced for non-invasive assessment of liver function in clinical setting as well as in experimental research. However, HBS is restricted to planar modalities in small animals since hepatic kinetics are generally too fast for SPECT acquisition. $^{99m}$Tc-GSA scintigraphy is an alternative, receptor mediated, non-invasive liver function test. After hepatic uptake, $^{99m}$Tc-GSA remains trapped in the liver, which readily enables additional SPECT for the assessment of both liver function and liver functional volume within one test. In this study we evaluate the use of $^{99m}$Tc-GSA scintigraphy combined with SPECT for the assessment of liver function and liver functional volume in normal and regenerating rat liver. Reproducibility of $^{99m}$Tc-GSA scintigraphy and SPECT was investigated by repeated measurements within the same rat. For the assement in a regenerating liver, liver function (99mTc-GSA uptake),liver functional volume (LFV) by 99mTc-GSA SPECT and conventional liver volume (LV) was assessed on 1, 3, 5 and 7 days (n=6 per time point) after 70% partial hepatectomy (PH).The correlation between repeated $^{99m}$Tc-GSA measurements was strong ($r = 0.75$, $p= 0.019$). In normal rat livers, there was a strong, significant correlation between LFV and LV ($r = 0.93$, $p< 0.0001$). The correlation between $^{99m}$Tc-GSA uptake and LV was moderate ($r = 0.62$, $p = 0.043$). Mean LFV and LV was significantly decreased 1 day after 70% PH, after which it regenerated to normal liver volume at day 5 and 7. There was a strong correlation between the LFV and LV in the regenerating liver ($r =0.86$, $p < 0.0001$). One day after 70% PH, the $^{99m}$Tc-GSA uptake significantly decreased compared to baseline after which it slowly increased to baseline level at day 7. During the regeneration process $^{99m}$Tc-GSA uptake was significantly lower compared to both LV ($p < 0.001$), and LFV ($p < 0.001$), when expressed as a percentage of baseline levels. 99mTc-GSA scintigraphy combined with SPECT is a feasible, non-invasive method for the assessment of hepatic functional volume in normal, as well as in regenerating rat livers. However, the hepatic $^{99m}$Tc-GSA uptake as a liver function test seems to underestimate the hepatic regeneration.

**Osteoclast-like Cell Formation from Peripheral Blood Mononuclear Cells of Chronic Liver Disease Patients with Osteopenia.**

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Osteoporosis is a common complication of chronic liver disease and the underlying mechanisms are not completely understood. In this study we aimed to determine if peripheral blood mononuclear cells (PBMCs) from chronic liver disease patients with osteopenia contain more activated T lymphocytes and whether osteoclast formation is favoured compared to controls. FACS analysis was performed for CD3/CD25/RANKL and CD14/CD11b. To asses mRNA expression of RANKL, RANK, OPG, M-CSF and TNF-$\alpha$ real time RT-PCR was conducted on PBMCs isolated at baseline. ELISA's were performed to detect levels of RANKL, OPG, M-CSF and TNF-$\alpha$ in plasma samples. Osteoclastogenesis assays were performed with the following culture conditions: (1) without addition of cytokines, (2) with M-CSF, (3) with M-CSF and OPG, (4) with M-CSF and RANKL. The activated T lymphocyte and monocyte populations were comparable for all three groups and RANKL expression was not detectable by FACS analysis. PBMCs from chronic liver disease patients with osteopenia formed more osteoclast–like cells which, when cultured in the presence of M-CSF and RANKL resorbed more bone than matched controls. Both the number of osteoclast-like cells and the amount of bone resorbed by these cells showed a correlation with the lumbar bone densities of the patients included in the study. Numbers of osteoclast-like cells were comparable between the four culture conditions in both patient groups, suggesting that in this culture system addition of M-CSF and/or RANKL is not a prerequisite for the formation of multinucleated cells. However, addition of M-CSF increased numbers of osteoclast-like cells in healthy controls. Plasma levels of M-CSF were increased in both patient groups compared to healthy controls, suggesting that osteoclast precursors were primed with higher levels of M-CSF. Our results show that circulating mononuclear cells from chronic liver disease patients with osteopenia have a higher capacity to become osteoclasts. This could partially be due to priming with higher levels of M-CSF in the circulation.

**Barrett's epithelium is associated with a specific bacterial flora in the esophagus**

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Persistent mucosal bacterial colonization may lead to chronic inflammation, a condition that is associated with development of neoplasia. Barrett's esophagus (BE) is a chronic inflammatory disorder and precursor of esophageal adenocarcinoma. Little is known on the bacterial flora in the esophagus and its association with BE.We aimed to determine whether BE is associated with a specific esophageal bacterial flora.Biopsies of esophageal squamous epithelium (SQ), BE, and gastric corpus (GC) were collected in 66 patients (M:F 2:1, mean age 57 yrs, range 22-89) with BE (histologically confirmed). Acridin Orange and modified Gram staining were performed to identify Gram negative and positive bacteria in the biopsies. A 16S rDNA micro-array analysis was performed to determine bacterial species per biopsy site.SQ predominantly contained Gram negative cocci, which were closely associated with the epithelial surface. In contrast, BE predominantly contained bacteria in the mucous layer and intestinal gland lumen, consisting primarily of Gram positive bacteria. GC contained smaller numbers with a similar distribution of the same bacteria. Micro-array analysis for 342 differential sequences showed the presence of >114 different species, primarily belonging to 5 phyla: Actinobacteria (n=16), Bacteroidetes (n=16), Firmicutes (n=57), Fusobacteria (n=5), and Proteobacteria (n=14). The bacterial population at each anatomic site was stable, and showed no significant variations between different patients (p=0.57). In contrast, a considerable difference was observed between the three different biopsy sites (p=0.03). A higher number of species was present (as mean percentage of total species per phylum) in SQ compared to BE for Actinobacteria (38% vs. 26%; p=0.04) and Bacteroidetes (55% vs. 45%; p=0.04), with BE versus GC showing borderline significance for Bacteroidetes (45% vs. 53%; p=0.05). Species diversity and bacterial density was higher in SQ compared to BE and GC. Strikingly, BE contained the highest density of Prevotella and Fusobacteria species.
Conclusion: Bacterial flora in BE is characterized by the presence of a specific bacterial flora, most notably containing Prevotella and Fusobacteria species. These known mucosal pathogens (e.g. in chronic peridontitis) may therefore play a role in the chronic inflammatory process of BE. This implicates that antibiotic treatment might be a therapeutic option in BE.

**The xenobiotic sensor PXR is associated with Barrett's esophagus**

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Reflux of gastroduodenal contents containing bile acids is thought to be compulsory for the development of Barrett's esophagus (BE). The Pregnane X Receptor (PXR) is an important factor in the detoxification of xenobiotic compounds. The continuous exposure of esophagus lining epithelium to refluxate may induce ectopic PXR expression, which may lead to downstream effects including development of BE. As PXR activity is in part determined at a genetic level, single nucleotide polymorphisms (SNPs) in the PXR gene may consequently play a role in susceptibility to BE. In this study we aimed to test for an association between PXR expression levels and BE.DNA was obtained from a total of 683 Caucasian subjects comprising 249 patients with BE, 233 patients with reflux esophagitis (RE), and 201 healthy controls. PXR haplotypes were based on the gene polymorphisms at -25358C/T, 7635A/G, and 8055C/T as determined by competitive allele specific PCR. PXR mRNA and protein levels in biopsies from squamous and columnar epithelium of patients with BE (n=8), squamous epithelium of RE patients (n=8), and controls (n=3) were determined by quantitative Real-Time PCR and immunohistochemistry.The PXR 7635G allele was more frequently observed in BE patients (128/462; 39%) than in RE patients (170/466; 36%) and controls (129/396; 33%) (BE vs controls: p=0.03; OR, 1.36; 95% CI, 1.03-1.80). The same trend was observed in allele distribution of the -25358 C/T and 8055C/T polymorphisms, but these were not statistically significant different between the groups. Columnar epithelium showed a 70-fold higher PXR mRNA expression level than squamous epithelium of the same BE patient (p=0.04). In addition, a 26-fold increase in PXR expression was found in RE when compared to controls (p=0.05). Immunohistochemical staining of BE tissue demonstrated that PXR was predominantly localized in the cytoplasm of columnar cells, and was more frequently present in villi than in crypts.
Conclusion: PXR alleles are associated with susceptibility to BE. The increased PXR expression observed during progression towards BE, suggests a role for in the detoxification of bile acids in BE. It remains to be established whether the handling of bile acids in the gastro-esophageal refluxate by PXR is involved in BE development or alternatively, in the increased risk of BE to develop esophageal adenocarcinoma.

## Germline hypermethylation of the MLH1 promotor region as the cause of Lynch syndrome

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Background: Hypermethylation of the MLH1 promoter region is most often a somatic event and associated with a high degree of microsatellite instability (MSI-H) in sporadic colorectal cancer (CRC). Recently several CRC cases with germline hypermethylation of the MLH1 promoter region were reported. In this study we studied the prevalence of MLH1 promoter hypermethylation in a large group of Lynch syndrome (HNPCC) suspected patients.Methods: From a group of 344 patients, that had (1) CRC < 50 yrs, and/or (2) endometrial cancer < 50 yrs, and/or (3) two or more Lynch syndrome associated cancers, irrespective of age, we selected those, who had no MLH1, MSH2 and MSH6 germline mutation and had absent MLH1 protein staining in the tumor or, if staining was unavailable, had MSI-H in the tumor. In these patients DNA from lymphocytes was tested for MLH1 promoter hypermethylation using methylation specific PCR (and sequencing) after sodium bisulphite modification and subsequently by denaturing gradient gel electrophoresis of the PCR products.Results: 59/344 patients were selected. Two (2/59=3.3%, 2/344=0.6%) had MLH1 promoter hypermethylation in lymphocytes. In both patients the family history for Lynch syndrome associated tumors was negative. Patient 1 had CRC at 37 yrs. The tumor showed MSI-H, loss of MLH1 protein staining and LOH for MLH1. DNA, isolated from skin fibroblasts, a mouth wash and the tumor also showed MLH1 promoter hypermethylation. DNA of the father, the mother and 7 siblings showed no MLH1 promoter hypermethylation. Patient 2 had five CRCs (48-60 yrs), endometrial cancer (52 yrs) and ureteral cancer (62 yrs). The tested tumors showed MSI-H.
Conclusion: Germline MLH1 promoter hypermethylation causes Lynch syndrome in a small percentage of Lynch syndrome suspected patients. This possibility should be considered in the evaluation of such patients.Supported by the Dutch Cancer Society RUG 2002-2678

**Effect of the immune response during the early phases of Barrett's Esophagus development**

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Little is known about the effect of the inflammatory response on the development of Barrett's esophagus (BE). It has been reported that Swiss Webster (SW) mice develop BE in a surgical reflux model. Since it is known that reflux esophagitis is characterized by a Th1 type and BE with a Th2 type immune response, we hypothesized that Th2 prone mice are more likely to develop BE. We therefore compared two different mouse strains, i.e. a Th1 prone (C57Bl/6) and a Th2 prone (SW) strain. Esophagojejunostomy and gastrectomy (GEJ-model) was performed in 8-week old male mice. Mice were sacrificed at 4, 8 and 16 weeks. Mucosal thickness of the esophagus, and distance to the anastomosis was determined in HE stained slides of the esophagus. In SHAM operated mice, the mean mucosal thickness of the esophagus was similar between the two strains (0.025 – 0.045 mm, p=0.89). In GEJ-mice, both an inflammatory reaction and an increase in the mucosal thickness of the esophagus was seen. At 16 weeks post GEJ, the mean longitudinal length of the inflamed tissue was significantly longer in SW mice than C57Bl/6 mice (respectively, 17.6 ± 1.4 mm vs. 6.4 ± 2.1 mm, p=0.002). The immune response was immunohistochemically analyzed using specific antibodies against B cells (B220), and T cells (CD3), T helper (Th, CD4) cells and cytotoxic T (Tc, CD8) cells.Both mice strains displayed a pronounced increase in the number of immune cells. The total number of Th (CD4) cells was higher in SW mice than in C57Bl/6 mice (1725 ± 270 vs. 879 ± 203 cells/mm$^2$, p=0.001). In C57Bl/6 mice, a mean increase in Th (CD4) cells was detected over time, i.e., a mean of 492 ± 94 cells/mm$^2$ at 4 weeks vs. 879 ± 203 cells/mm$^2$ at 16 weeks (p=0.14), which was not observed in SW mice. SW mice esophagus had more B cells compared with C57Bl/6 mice at all time points (i.e. 204 ± 40 vs. 29 ± 15 cells/mm$^2$ at 16 weeks, p=0.003). Similar results were found for eosinophils and T (CD3) cells between the two strains.
Conclusions: The Th2-prone SW mice showed a more pronounced inflammation in response to chronic reflux than the Th1 prone C57Bl/6 mice, as indicated by the increased mucosal thickness and higher numbers of infiltrating Th2-associated immune cells. Thus, the type of immune response, Th1 vs. Th2, elicited by the host to chronic reflux does result in an distinct local immune pathology which may affect the time of onset of BE.

**Predisposition to the Th1 immune response is associated with an increased risk for development of Barrett's esophagus**

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Previously we found that the transition from reflux esophagitis (RE) to Barrett's esophagus (BE) is associated with a shift from a cellular (Th1) towards a humoral (Th2) immune response. These findings suggest that a Th1 response is involved in BE development, whereas a Th2 response is more important to maintain the chronic status of BE.In this study we aimed to determine the function of the immune responses (Th1 versus Th2) for the initiation and chronic phase of BE.Duodenal reflux was induced by gastrectomy with esophagojejunostomy (GEJ) in 7 week-old male Lewis rats (Th1 prone; n=18), Brown Norway (BN; Th2 prone; n=18), and Wistar rats (combined Th1/Th2 prone; n=18). Rats were sacrificed at various time-intervals until 6 months after GEJ. Metaplasia and inflammation in the esophagus were determined by HE staining and immuno-histochemistry with the markers CD63 and CD168 (macrophages), CD3 (T cells), CD8 (cytotoxic T cells), CD45RA (B cells), CDX2 (intestinal epithelium), and PAS (goblet cells).At 2 wks post GEJ, all strains had developed esophageal hyperplasia and severe esophagitis, characterized by the influx of macrophages and CD8+ T cells. At 5 wks, BE characterized by intestinal metaplasia (CDX2 expression) with goblet cells (PAS) was observed in the distal esophagus of BN and Lewis rats. At 9 wks, all strains had developed BE in the distal esophagus, and hyperplasia with ulceration was observed throughout the proximal esophagus. Lewis rat's esophagus showed the highest concentration of T and B cells. At 12 weeks, the BE segment had further increased in Lewis and BN rats. The acute and severe esophagitis in the proximal esophagus was characterized by large numbers of macrophages and T cells, while the inflammation in the BE segment was more chronic involving B cells. At 6 months, all strains had developed BE, but this was most extended in the Th1 prone Lewis rats, with a patchy pattern of BE found along the whole length of the esophagus.
Conclusion: Prior to BE development, Th2 prone rats also develop a Th1 inflammatory response and, vice versa, Th1 prone rats display a Th2 type reaction in the BE segment. The Th1 immune status of Lewis rats results in a faster development of BE. This suggests that while BE patients have a Th2 type chronic inflammation in the esophagus, patients with a Th1 immune status might be more susceptible to the development of BE than Th2 prone patients.

## Regulation of the murine Muc2 mucin gene by HNF-3 factors*

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The secretory mucin Muc2, a goblet cell marker, is the major structural component of intestinal mucus and thus plays an important role in maintaining intestinal homeostasis. This mucin has a spatio-temporal pattern of expression during intestinal development and goblet cell differentiation. However, the molecular mechanisms governing its expression during these biological processes are still poorly understood. We previously identified a cis-element for the hepatocyte nuclear factor-3alpha (HNF-3$\alpha$) and -3beta (HNF-3$\beta$) transcription factors next to an important GATA-4 regulatory element. Since HNF-3$\alpha$ and HNF-3$\beta$ participate in transcriptional programs governing intestinal cell differentiation, we undertook to study their role in Muc2 regulation. Immunohistochemical studies in the mouse small intestine showed co-localisation of HNF-3$\alpha$ and HNF-3$\beta$ in Muc2-expressing goblet cells. Those two factors were also expressed in the murine CMT-93 colorectal cancer cell line that was used for our transcriptional studies. Gene targeting using RNA interference approach demonstrated that both transcription factors regulate Muc2 transcription. In vivo binding of HNF-3$\alpha$ and HNF-3$\beta$ to the Muc2 promoter was assessed by chromatin immunoprecipitation assay. Co-transfections experiments with wild-type and mutated forms (for the four HNF3 elements) of the proximal promoter of Muc2 indicated that these four HNF3 elements are necessary to convey Muc2 transcriptional activation. We did not find synergistic activity between GATA-4 and HNF-3$\alpha$/3$\beta$ in the proximal promoter. Conclusion: Altogether these results identify Muc2 as a new target of HNF-3$\alpha$ and HNF-3$\beta$ and point out an important role for these transcription factors in Muc2 expression in the intestine during development and goblet cell differentiation.

**Her-2/neu amplification in esophageal adenocarcinoma as a potent target for cancer immunotherapy.**

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Her-2/neu is a 185KDa protein receptor which is largely overexpressed through gene amplification in several cancers. Her-2/neu protein has been proven to be an ideal Tumor Associated Antigen (TAA) for immunotherapies. T-cell transfer therapies with anti Her-2/neu CTL populations have confirmed significant tumor response for instance against breast cancer. In previous studies we found that Her-2/neu is amplified and overexpressed in at least 50% of esophageal adenocarcinomas. It is known that the outcome of esophageal cancer is poor and novel treatment strategies are urgently requested. Therefore, developing Dendritic Cell (DC) or T-cell transfer immunotherapy by mediating CTL responses against Her-2/neu would be an attractive strategy as an alternative treatment for esophageal adenocarcinomas. AIM: To assess whether loading Dendritic Cells (DCs) with full length Her-2/neu mRNA is feasible to raise specific CTL populations that can be used for future immunotherapeutic strategies. MATERIALS AND METHODS: Her-2/neu mRNA was generated using the plasmid pSPJC1, with an insert coding for Her-2 /neu which allows in vitro transcription under the control of an SP6 promoter. Patient's monocytes were electroporated with Her-2/neu mRNA and matured into DCs. Hereupon, DCs were analysed for the expression of the Her-2/neu protein, for maturation markers and for their potential to secrete IL-12 and IL-10. Mature DCs were subsequently used to stimulate patient's lymphocytes in a Mixed Lymphocyte Reaction (MLR) to assess lymphocyte proliferation by measuring incorporation of [$^3$H] thymidine and using liquid scintillation counting. Expression of IFN-γ was performed by using CBA. RESULTS: The mature DCs highly expressed maturation markers such as CD80, CD86, CD83, CD209, and CCR7, and were able to release sufficient amounts of IL-12 but low IL-10, features that demonstrate their high potential for inducing CTL reponses. Her-2/neu expression was detected after one week of culture in the mature DCs. Stimulation of the patient's lymphocytes by the Her-2/neu RNA loaded DCs resulted in high T-cell proliferation (CTL response) with significantly higher IFN-γ production as compared to lymphocytes stimulated by the not loaded DCs (control).
Conclusion: This study demonstrates that the full length Her-2/neu RNA can be used for generating DC mediated specific T-cell populations. These CTL populations could be expanded ex vivo and employed for future T-cell transfer therapies for esophageal cancer patients with Her2/neu amplification. Alternatively, DCs loaded with full length Her2/neu RNA can be employed to treat esophageal adenocarcinomas with DC vaccination immunotherapy.

## Identification of biological pathways involved in colon adenoma to carcinoma progression

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Colorectal cancer (CRC) is the second leading cause of cancer death in the western world. It is generally accepted that CRC arises from premalignant lesions - adenomas. Adenomas and carcinomas differ in terms of genomic alterations. The aim of this study was to identify which biological pathways are differentially expressed between colon adenomas and carcinomas. A dataset of 34 adenomas and 30 carcinomas from which microarray-expression data had been obtained previously, were analyzed by the web program Pathway Level Analysis of Gene Expression (PLAGE). PLAGE identifies differentially expressed groups of genes from a collection of predefined gene sets by comparing the activity levels of each pathway among two sample groups. The program offers the possibility to include 135 predefined KEGG (Kyoto Encyclopedia of Genes and Genomes) and 259 Biocarta pathways, as well as custom defined pathways. In the present study we included, in addition to the KEGG and Biocarta pathways, several expression signatures published in literature that originated from experimental (microarray expression) data regarding different biological processes and entities. Data analysis by PLAGE using only the predefined KEGG and Biocarta pathways, revealed several pathways that were significantly differentially expressed between colon adenomas and carcinomas. Most of these pathways were involved in amino acid and lipid metabolism. When experimental derived expression signatures were included in the PLAGE-analysis, significant differences were found in five out of ten signatures tested. An expression signature that discriminated colorectal adenomas from carcinomas described by Lin et al (2002), also turned out to be significant in our data set ($p<0.0001$). Moreover, significant differences were observed for two chromosomal instability signatures (Carter et al, 2006) - CIN25 ($p=0.0001$) and CIN70 ($p<0.0001$), a proliferation signature (Whitfield et al, 2006; $p=0.0001$), as well as a metastazation signature (Li et al, 2006; $p<0.0001$). To our knowledge none of these pathways were previously tested in colorectal tumors. Compared to the KEGG and Biocarta pathways, these five experimental derived pathways all rank in the top 15 significant pathways. Taken together, colorectal adenoma to carcinoma progression is associated with significant changes in gene expression levels in multiple cancer associated biological processes like proliferation, metastatic potential and chromosomal instability.

**De novo FoxP3 expression in mucosal regulatory T cells that are generated through mucosal antigen application***

M.F. du Pré[1], L.A. van Berkel[1], W.W.J. Unger, F. Hauet-Broere, E.E.S. Nieuwenhuis[1], G. Kraal, J.N. Samsom[1]. Dept of Paediatrics[1], division Gastroenterology and nutrition Erasmus MC – Sophia Children's Hospital, Rotterdam, The Netherlands

In mice, oral or nasal application of OVA leads to antigen specific suppression of both DTH and IgE responses. This tolerance can be transferred to naive recipients by $CD4^+$ regulatory T cells ($T_R$) from the spleen. These mucosal $T_R$ function irrespective of cytokine polarization and exert systemic suppression through "infectious" tolerance by passing their tolerizing capacity on to naive T cells. Phenotypic analysis of these $CD4^+$ $T_R$ revealed that they are present in both $CD25^+$ and $CD25^-$ T cell subsets, although, in contrast to the $CD25^+$ T cell subset, suppression by the $CD25^-$ $T_R$ population is antigen-specific. To unravel where naive $CD4^+$ T cells differentiate into these specialized antigen specific $CD25^-$ $T_R$ during oral and nasal tolerance, we followed the fate of transferred OVA T-cell-receptor transgenic DO11.10 cells in vivo. We demonstrate that within 48 h after mucosal OVA application, $CD4^+$ DO11.10 T cells divide in the mucosa draining LN and can transfer tolerance to naive recipients. As such, these data demonstrate that, in contrast to naturally occurring $T_R$, mucosally induced $T_R$ are adaptive and differentiate from naive T cells within the mucosa draining LN. As there is controversy regarding the question whether adaptive $T_R$ also express the regulatory transcription factor FoxP3, which is considered a hallmark for naturally occurring $T_R$, we wished to investigate whether mucosally induced $T_R$ express FoXP3 upon differentiation in absence of naturally occurring $T_R$. Thereto, using flow cytometry, we followed FoxP3 protein expression during mucosal differentiation of OVA T-cell-receptor transgenic DO11.10 cells from mice on a $RAG^{-/-}$ background. Crucially, we observed that upon differentiation in the mucosal LN naive T cells are converted to FoxP3 expressing T cells. FoxP3 expression was heterogeneïc and already initiated within the first division. We hypothesize that intrinsic capacities of the draining LN mediate expression of FoxP3 during mucosal $T_R$ differentiation and are currently investigating their nature.
In conclusion, these data establish that mucosal tolerance is mediated by the induction of specialized adaptive mucosal $T_R$ that differentiate locally in mucosa draining LN and *de novo* express FoxP3. Our findings provide crucial new insights for the understanding of chronic intestinal diseases such as Celiac Disease and Inflammatory Bowel disease, which are characterized by loss of mucosal tolerance.

## ALFABETISCHE LIJST VAN STANDHOUDERS VOORJAARSCONGRES 2007

B = Beneluxhal
K = Kempenhal

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Plattegrond expositie

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**Werkadres**
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Doctoraalexamen : ja/neen*; zo ja, welke studierichting:
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**Tevens wil ondergetekende zich aansluiten bij:**
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