Programma voorjaarsvergadering 18 en 19 maart 2004

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

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VOORWOORD

Hierbij treft u het volledige programma aan van de voorjaarsvergadering op 18 en 19 maart 2004 te Veldhoven. Het programma zal dit jaar op donderdag wat eerder van start gaan, namelijk om **13.00 uur**. Ook op vrijdag zijn de tijden enigszins gewijzigd, zie hiervoor het programma.

Naast vrije voordrachten van de Nederlandse Vereniging voor Gastrointestinale Chirurgie, de Sectie Neurogastroenterologie en Motiliteit (voorheen de Sectie Maagdarmmotoriek) en de Nederlandse Vereniging voor Hepatologie, worden op donderdagmiddag nog drie symposia verzorgd.

In de Brabantzaal het symposium getiteld: *'Morbide Obesitas: Wat moeten we ermee?*' Voorts een door NESPEN georganiseerd symposium over *'Biomarker development and proteomic strategies'* in de Baroniezaal en een klinisch symposium van de NVH in de Parkzaal, getiteld: *'Hepatocellular Carcinoma'* .
Daarnaast weer presentaties van door de MLDS gesubsidieerde projecten: vanaf 17.00 uur zijn er drie voordrachten te beluisteren in de Brabantzaal.

Tijdens de plenaire avondsessie, die op donderdagavond om 20.00 van start gaat met de President Selection, zal de Altana lecture worden verzorgd, ditmaal door Prof. dr. G. van Asche uit Leuven over het onderwerp chronische anemie. Alle leden worden van harte uitgenodigd hierbij aanwezig te zijn!

Op vrijdag zijn er sessies met vrije voordrachten van de Sectie Gastrointestinale Endoscopie, de Nederlandse Vereniging voor Gastroenterologie en de Sectie Experimentele Gastroenterologie.
In de Brabantzaal zal Prof. dr. R. Fodde om 09.30 uur de Frieda den Hartog Jager lecture houden met een voordracht getiteld: *'Stamcellen, signaaltransductie, genetische instabiliteit en darmkanker: it's all in the game'*

In de Diezezaal is er in de ochtend het programma van de Vereniging Maag Darm Lever Verpleegkundigen en in de middag een sessie, georganiseerd van de Sectie Endoscopie Verpleegkundigen en Assistenten.

Belangrijk voor 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.

Tenslotte nog graag even uw aandacht voor het volgende:
Wilt u op de dag van vertrek vóór 09.00 uur uw kamersleutel inleveren bij de receptie? Voorts verzoeken wij u af en toe op de monitoren in het congrescentrum te kijken in verband met eventuele berichten.

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

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

Programma donderdag 18 maart 2004

DONDERDAG	BRABANTZAAL	BARONIEZAAL	PARKZAAL	DIEZEZAAL
13.00-15.00	Vrije voordrachten Nederlandse Vereniging voor Gastrointestinale Chirurgie p. 7-8	NESPEN symposium *'Biomarker development and proteomic strategies'* Gevolgd door vrije voordrachten v.a. 14.30 uur p. 9-10	Vrije voordrachten Nederlandse Vereniging voor Hepatologie p. 12	Op donderdag geen programma in deze zaal
15.00-15.30	Theepauze	Theepauze	Theepauze	
15.30-17.00	**Symposium:** Morbide *Obesitas: Wat moeten we ermee?* (NVGE-NVGIC) p. 8 Presentaties projecten Maag Lever Darm Stichting p. 9	Vrije voordrachten Netherlands Society of Parenteral and Enteral Nutrition p. 10-11	Vervolg vrije voordrachten Nederlandse Vereniging voor Hepatologie **Symposium: '***Hepato-cellular Carcinoma'* (v.a. 16.20 - 18.10 uur) p. 13-14	
17.30-20.00	Congresborrel gevolgd door diner (Diezezaal)	Congresborrel gevolgd door diner (Diezezaal)	Congresborrel gevolgd door diner (Diezezaal)	
20.00-21.30	**Presidential selection** **Altana Lecture door Prof. dr. G. van Asche (Leuven, België)**	-	-	
21.30-22.00	Ledenvergadering NVGE	-	-	

Programma vrijdag 19 maart 2004

VRIJDAG	BRABANTZAAL	BARONIEZAAL	AUDITORIUM	DIEZEZAAL
08.00	Casuïstiek voor de klinikus en vrije voordrachten p. 15	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie (aanvang 08.30) p. 17		
09.00 09.30	Vrije voordrachten Sectie Endoscopie p. 15 *Frieda den Hartog Jager lecture Prof. dr. R. Fodde* p. 15	Vervolg voordrachten NVGE Vrije voordrachten Sectie Experimentele Gastroenterologie p.18-19	Vrije voordrachten Sectie Neurogastroenterologie en Motiliteit p. 19-20	Programma Vereniging Maag Darm Lever Verpleegkundigen p. 26
10.00	Koffiepauze	Koffiepauze	Ledenvergadering	Koffiepauze
10.30	**Symposium:** *'Endo-echografie in Nederland. Hoe, bij wie en door wie?'* p. 16	International Teaching Session p. 19	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie p. 21	Programma Vereniging Maag Darm Lever Verpleegkundigen p. 26
12.00	Lunch	Lunch	Lunch	lunch
13.30	Vrije voordrachten Sectie Gastro-intestinale Endoscopie p. 22-23	Vrije voordrachten Sectie Experimentele Gastroenterologie p. 23-24	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie p. 25-26	Programma Sectie Endoscopie Verpleeg-kundigen en Assistenten p. 27
15.00	Theepauze / einde alle programma's	Theepauze / einde alle programma's	Theepauze / einde alle programma's	Theepauze / einde alle programma's

CURSORISCH ONDERWIJS IN MAAG-DARM-LEVERZIEKTEN **AUDITORIUM**
17 en 18 MAART 2004

Cursuscommissie:	Dr. C.J.H.M. van Laarhoven (chirurg, Elisabeth Tilburg) Dr. B.P.L. Wijnhoven (AGIO Heelkunde, Erasmus MC) Dr. H.M. van Dullemen (MDL, AZG) Dr. C.M.F. Kneepkens (KA, AZVU) Dr. I.A.M. Gisbertz (MDL i.o., UMCN) Prof. Dr. C.J.J. Mulder (voorzitter) (MDL, VUMC)

Woensdag 17 maart 2004

20.30 - 20.50 uur	Short Bowel Syndroom: wat komt eraan Prof. dr. P.B. Soeters, Heelkunde, AZM
21.00 - 21.20 uur	Sondevoeding: waar, wie, wat ? Dr. G.R. Swart, Interne II, Erasmus MC
21.30 - 21.50 uur	Parenterale thuisvoeding Dr. A.H.J. Naber, MDL, UMCN
22.00 - 22.20 uur	Anorexia nervosa, wie speelt 1e viool ? Drs. A.A. van Elburg, jeugdpsychiater, UMCU

Donderdag 18 maart 2004

08.00 - 08.20 uur	Hypoalbuminemie: substitutie voor OK ? Wanneer ? Dr. W.G. Gemert, chirurg AZM
08.30 - 08.50 uur	Dunne darm transplantatie Drs. G. Dijkstra, MDL, AZG
09.00 - 09.20 uur	MRI pancreas Prof. dr. J.O. Barentsz, Radiologie, UMCN
09.30 - 09.50 uur	Pijnbestrijding pancreas Prof. dr. J.B.M.J. Jansen, MDL, UMCN
koffiepauze	
10.30 - 11.00 uur	Genetica van chronische pancreatitis Dr. J.P.H. Drenth, MDL, UMCN
11.10 - 11.30 uur	Pancreassubstitutie Dr. M.J. Bruno, MDL, AMC
11.40 - 12.00 uur	Necrotiserende pancreatitis H. Friess, Heelkunde, Heidelberg
12.10 - 12.30 uur	Timing resectie chronische pancreatitis Prof. dr. H.G. Gooszen, Heelkunde, UMCU

De cursuscommissie verwacht van de MDL-artsen i.o. dat ze de Cursus Klinische Hepatologie van de Nederlandse Vereniging voor hepatologie éénmaal bezoeken in de eerste drie jaar van de opleiding en minimaal éénmaal in het tweede deel van de MDL-opleiding.
Binnen het blok voeding wordt normaliter morbide obesitas behandeld. Graag attenderen wij u op het middagsymposium op 18 maart 2004 over dit onderwerp (Brabantzaal, aanvang 15.30 uur, zie pag. 8)

Nederlandse Vereniging voor Gastrointestinale Chirurgie **Brabantzaal**

12.30 Inschrijving, koffie

Voorzitters: C.J.H.M. van Laarhoven en S.A. Koopal

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

13.00 Endotoxin-related complications after systemic hypotension are effectively reduced by a lipid-rich enteral nutrition in bile duct-ligated rats. *(p. 28)*
M.D.P. Luyer[1], W.A. Buurman[1], M. Hadfoune[1], J.A. Jacobs[2], C.H.C. Dejong[1], J.W.M. Greve[1]. Dept of Surgery[1] and Medical Microbiology[2], University of Maastricht and University Hospital Maastricht, The Netherlands

13.10 Subtotal Colectomy Does Not Reduce Pancreatic Infection in Experimental Acute Pancreatitis. *(p. 29)*
L.P. van Minnen[1], V.B. Nieuwenhuijs[1], M.T. de Bruijn[1], M.R. Visser[2], L.M.A. Akkermans[1], H.G. Gooszen[1]. Depts of Surgery[1] and Microbiology[2], University Medical Center, Utrecht, The Netherlands

13.20 Experienced problems and expected professional care in patients after surgery for esophageal cancer. *(p. 30)*
E.M.L. Verschuur, T.C.K. Tran, E. J. Kuipers, H.W. Tilanus, P.D. Siersema. Dept of Gastroenterology and Hepatology, Erasmus MC, Rotterdam, The Netherlands

13.30 Poor quality of life after colon interposition compared to gastric tube for esophageal cancer replacement. *(p.31)*
H.A. Cense[1], M.R.M. Visser[2], A.G.E.M. de Boer[2], J.W. van Sandick[1], B.Lamme[1], H.Obertop[1], J.J.B. van Lanschot[1]. Depts of Surgery[1], and of Medical Psychology[2] Academic Medical Center at the University of Amsterdam, Amsterdam, The Netherlands

13.40 Five years results of the Manchet I trial: Randomised Controlled Trial of Laparoscopic versus Open Nissen Fundoplication. *(p.32)*
H.G. Gooszen, J.E. Bais, H. Rijnhart-de Jong. On behalf of the Dutch National Antireflux Surgery Study Group

13.50 Vagus nerve injury after antireflux surgery. *(p. 33)*
A.A.M. Masclee[1], C. Noomen[1], C de Jong[1], J Ringers[2], CBHW Lamers[1]. Depts of Gastroenterology-Hepatology[1] and Surgery[2]; Leiden University Medical Center

14.00 Influence of Hospital Volume on Mortality in Pancreaticoduodenectomy: a Meta-analysis. *(p.34)*
N.T. van Heek, R.C.I. van Geenen, S.S.M. de Castro, H. Obertop, D.J. Gouma. Dept of Surgery, Academic Medical Center, Amsterdam, The Netherlands

14.10 Thoracoscopic splanchnicectomy: Technique and results in 72 patients with chronic pancreatitis. *(p.35)*
H.C.J.L. Buscher, J.B Janssen[1], R.P. Bleichrodt and H.van Goor. Dept. of Surgery and Dept. of Gastroenterolgy[1], University Medical Center Nijmegen

14.20 Chronic mesenteric ischemia: from classical abdominal angina to single- and multivessel disease; experience in 102 patients. *(p. 36)*
P.B.F. Mensink[1], J.J. Kolkman[1], A.S. van Petersen[2], A.B. Huisman[3], E.J. Kuipers[4], R.H. Geelkerken[2]. Dept of Gastoenterology[1], Vascular Surgery[2] and Interventional Radiology[3], Medisch Spectrum Twente, Enschede. Dept of Gastroenterology[4], Erasmus Medical Center, Rotterdam, The Netherlands

14.30 Laparoscopic-assisted versus open ileocolic resection for Crohn's disease: a randomized trial. *(p.37)*
S. Maartense[1], M.S. Dunker[1], J.F. Slors[1], M.A. Cuesta[2], E.G.J.M. Pierik[3], D.J. Gouma[1], S.J. van Deventer[4], A.A. van Bodegraven[5], and W.A. Bemelman[1]. Dept of Surgery Academic Medical Center Amsterdam[1], Dept of Surgery Vrije Universiteit Medical Center[2], and Dept of Surgery Isala Clinics Zwolle[3], Dept of Gastroenterology Academic Medical Center Amsterdam[4] and Dept of Gastroenterology Vrije Universiteit Medical Center[5], The Netherlands

14.40 Poor condition at operation is an independent risk factor in long-term survival of colo-rectal cancer patients. *(p.38)*
R.P.M. Brosens[1], J.L.T.Oomen[1], A.S.Glas[1], A.F.Engel[1]. Dept of Surgery[1], Zaans Medical Centre[1], The Netherlands

14.50 TEM versus TME in early rectal cancer: a prospective comparative study. *(p.39)*
P.G.Doornebosch[1], R.A.E.M. Tollenaar[2], E. Meershoek-Klein Kranenbarg[2], A.C. de Boer[3], C.J.H. van de Velde[2], E.J.R. de Graaf[4]. Dept of General Surgery[1], Rijnland Hospital, Leiderdorp, Dept of General Surgery[2], Leiden University Medical Center, Leiden, Dept of Internal Medicine[3] IJsselland Hospital, Capelle a/d IJssel, Dept of General Surgery[4], IJsselland Hospital, Capelle a/d IJssel, The Netherlands

15.00 Theepauze

Nederlandse Verenigingen voor Gastroenterologie en Gastrointestinale Chirurgie Brabantzaal

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Voorzitters: J.W.M. Greve en E.M.H. Mathus-Vliegen

15.30 **Symposium: Morbide Obesitas: Wat moeten we ermee?**

Epidemiologie: Wat staat ons te wachten?
Prof. dr. J. Seidell, epidemioloog, Vrije Universiteit Amsterdam en VUmc

Behandeling van obesitas: Wat heeft de medicus practicus te bieden?
Prof. dr. E.M.H. Mathus-Vliegen, maag-darm-leverarts, AMC, Amsterdam

Chirurgische opties: technieken en resultaten
Dr. J.W.M. Greve, chirurg, AZM, Maastricht

De lap-band: resultaten, complicaties en functionele sequelae
Dr. B. van Ramshorst, chirurg, St. Antonius Ziekenhuis, Nieuwegein

Welke complicaties zijn van belang voor de maag-darm-leverarts/endoscopist: diagnostiek en behandeling
Dr. B.L.A.M. Weusten, maag-darm-leverarts, St. Antonius Ziekenhuis, Nieuwegein

17.00 Einde symposium

Presentaties projecten Maag Lever Darm Stichting **Brabantzaal**

Voorzitter: J.B.M.J. Jansen

17.00 The impact of (treatment for) rectal cancer on quality of life and societal functioning
(Final report Maag Lever Darm Stichting project SWO 02-15). *(p.40)*
A.M. Stiggelbout, C.A.M. Marijnen, M. van den Brink, H. Putter, E. Klein Kranenbarg, C.J. van de Velde; on behalf of the Dutch Colorectal Cancer Group. Depts of Medical Decision Making, of Surgery, and of Clinical Oncology, Leiden University Medical Center, The Netherlands

17.10 Experienced problems in daily life by HPN-dependent patients
(Final report Maag Lever Darm Stichting project SWO 01-16). *(p.41)*
A. Persoon[1], L. Schoonhoven[1], T. Naber[2], H. Sauerwein[3], T. van Achterberg[1]. Dept of Nursing Science[1], Dept of Gastroenterology[2], University Medical Center St. Radboud, Nijmegen, Dept of Endocrinology and Metabolism[3], Academic Medical Center Amsterdam, The Netherlands

17.20 Irritable Bowel Syndrome: towards an integrated psycho-neurophysiological approach
(Final report Maag Lever Darm Stichting project WS 99-17). *(p.42+43)*
P.P.J. van der Veek[1], Y.R. van Rood[2], C.A. Swenne[3], I. Biemond[1], F. Zitman[2], Ph. Spinhoven[2] and A.A.M. Masclee[1], Depts of Gastroenterology and Hepatology[1], Psychiatry[2] and Cardiology[3], Leiden University Medical Center, Leiden, The Netherlands

17.30 Einde programma in deze zaal.
Congresborrel in expositiehal en aansluitend diner in de Genderzaal.

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

12.30 Ontvangst, inschrijving, koffie

Voorzitters: N.E.P. Deutz en R.J. Vonk

Symposium 'Biomarker development and proteomic strategies'

13.00 Application of various proteomics techniques
R. Bisschoff, Centre for Pharmacy, Dept. Bioanalysis and Toxicology, University of Groningen

13.18 Biomarkers and 2D-gels
J. Renes, Maastricht Proteomics Center, Dept. Human Biology, University of Maastricht

13.36 High-throughput proteomics in biomedical research
H. Roelofsen, Dept. of Nutrition and Metabolism, Paediatric Laboratory, Academic Hospital Groningen

Donderdag 18 maart 2004

13.54 Identification of biomarkers (Q-star)
H. Aerts

14.12 Identification of biomarkers (FT-MS)
Th. Luider

14.30 Einde symposium

Voorzitters: C.H.C. Dejong en P. Voshol

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

14.30 Discrepancy between prescribed and administered energy in patients totally dependent on tube feeding. *(p.44)*
P.W.J.H. van den MSc[1], Dr. A.H.J. Naber[2], Ir. E.L. Rasmussen-Conrad[1]. Dept of Dietetics[1] and Dept of Gastroenterology[2] University Medical Centre Nijmegen, The Netherlands

14.40 Psychosocial problems in long-term HPN dependent patients. *(p.45)*
G. Huisman[1], A. Persoon[1], L. Schoonhoven[1], T. Naber[2]. Dept of Nursing Science[1] and Dept of Gastroenterology[2], University Medical Centre St. Radboud, Nijmegen, The Netherlands

14.50 Randomised controlled trial of glutamine-enriched enteral feeding in very low birth weight infants: effect on clinical outcome *****. *(p.46)*
R.M. van Elburg, A. van den Berg, H.N. Lafeber, and W.P.F. Fetter. Dept of Pediatrics, VU University Medical Center, Amsterdam, The Netherlands

15.00 Theepauze

15.30 Amino acid administration directly from birth onwards in very low birth weight (VLBW) infants is safe and results in anabolism *****. *(p.47)*
C.H.P. van den Akker[1], F.W.J. te Braake[1], D.L. Wattimena[2] and J.B. van Goudoever[1]. Dept of Neonatology[1], Sophia Childrens Hospital, Erasmus MC, Rotterdam, Mass Spectrometry Lab[2], Erasmus MC, Rotterdam, The Netherlands

15.40 High intestinal utilization of threonine in piglets *****. *(p.48)*
M.W. Schaart[1], S.R.D. van der Schoor[1], H. Schierbeek[1], B. Stoll[2], D.G. Burrin[2], J.B. van Goudoever[1,2]. Dept of Pediatrics, Div. of Neonatology[1], ErasmusMC/Sophia Children's Hospital, Rotterdam, the Netherlands and Dept of Pediatrics[2], USDA/ARS Children's Nutrition Research Center, Baylor College of Medicine, Houston, USA

15.50 Presence of non-cachectic tumour prohibited the post-operative rise in arginine and NO production in vivo in mice. *(p.49)*
Y.L.J. Vissers, M.F. von Meyenfeldt, Y.C. Luiking, C.H.C. Dejong, N.E.P. Deutz. Dept of Surgery, Nutrition and Toxicology Research Institute Maastricht, Maastricht University, The Netherlands

16.00 In vivo glutathione synthesis measurements in human liver and muscle; comparison between weight losing and non-weight losing cancer patients. *(p.50)*
M.C.G. van de Poll[1], Y.C. Luiking[1], S.J. Wigmore[2], J.W.M. Greve[1], P.B. Soeters[1], N.E.P. Deutz[1], K.C.H. Fearon[2], C.H.C. Dejong[1], Depts. of surgery, Maastricht University, the Netherlands[1] and Royal Infirmary Edinburgh, Scotland[2]

16.10 Vagal Stimulation Attenuates Muscularic Inflammation and Post-operative Ileus Induced by Intestinal Manipulation. *(p.51)*
W.J. De Jonge[1], F.O. The[1], D. van der Coelen[1], D.J. van Westerloo[2], K.J. Tracey[3], S.J. van Deventer[1], R.H. van den Wijngaard[1], G.E. Boeckxstaens[1]. Depts of Gastroenterology and Hepatology[1] and Experimental Internal Medicine[2], Academic Medical Centre, Amsterdam, Lab of Biomedical Sciences[3], New York, Unites States

16.20 Low dose ileal oil perfusion increases satiety in humans. *(p.52)*
T. Symersky[1], B.C. Kee[1], E.Haddeman[2], H.P.F. Peters[2], A.A.M. Masclee[1]. Dept. of Gastroenterology and Hepatolgy[1], Leiden University Medical Center, Leiden and Unilever Health Institute[2], Unilever Research, Vlaardingen, the Netherlands

16.30 Effect of intravenous PYY infusion on pancreatico-biliary secretion. *(p.53)*
T. Symersky[1], M. Frölich[2], I. Biemond[1], A.A.M. Masclee[1]. Dept. of Gastroenterolgy and Hepatology[1] and Clinical Chemistry[2], Leiden University Medical Center, Leiden, the Netherlands

16.40 Modulation of gene expression by vegetables in normal colorectal mucosa of sporadic colon adenoma patients and healthy controls. *(p.54)*
S.G.J. van Breda[1], E. van Agen[1], L.G.J.B. Engels[2], E.J. Moonen[1], J.C.S. Kleinjans[1] and J.H.M. van Delft[1]. Dept of Health Risk Analysis and Toxicology[1], University of Maastricht, Maastricht, Dept of Gastroenterology[2], Maasland Hospital Sittard, Sittard, The Netherlands

16.50 Apolipoprotein C3-deficiency results in Diet-induced Obesity and Insulin Resistance in Mice. *(p.55)*
I. Duivenvoorden[1], B. Teusink[1], J.A. Romijn[2], L.M. Havekes[1,3] and P.J. Voshol[1,2]. Div. Biomedical Research[1], TNO Prevention and Health, Leiden, The Netherlands
Depts. of Endocrinology and Metabolic Diseases[2], Internal Medicine and Cardiology[3] Leiden University Medical Center, The Netherlands

17.00 Intracerebroventricular Neuropeptide Y infusion precludes inhibition of glucose and VLDL-production by insulin. *(p.56)*
A.M. van den Hoek[1,2], P.J. Voshol[1,3], B.N. Karnekamp[1], R.M. Buijs[4], J.A. Romijn[3], L.M. Havekes[1,2,5] and H. Pijl[2,3]. Division Biomedical Research[1] TNO-Prevention and Health, , Leiden, Depts of Internal Medicine[2], Endocrinology and Metabolic Diseases[3] and Cardiology[5] Leiden University Medical Center, Netherlands Institute for Brain Research[4], Amsterdam, The Netherlands

17.10 Altered Tissue-Specific VLDL-derived Fatty Acid Partitioning may be Involved in the Ritonavir-Associated Lipodystrophy Syndrome. *(p.57)*
M. den Boer[1,2], J.A. Romijn[2], P. Reiss[4], M. van der Valk[4], P.J. Voshol[1,2], L.M. Havekes[1,3]. Div. Biomedical Research[1], TNO Prevention and Health, Leiden, Depts of Endocrinology and Metabolic Diseases[2] and Internal Medicine and Cardiology[3], Leiden University Medical Center, Dept of Infectious Diseases[4], Tropical Medicine and AIDS, AMC, Amsterdam, The Netherlands

17.20 24 Hours Fasting Differentially affects Hepatic and Muscle Insulin Sensitivity. *(p.58)*
A.C. Heijboer[1,2], E. Donga[1], L.M. Havekes[1,3], J.A. Romijn[2], E.P.M. Corssmit[2], P.J. Voshol[1,2]. Div. Biomedical Research[1] TNO Prevention and Health, Leiden,
Depts of Endocrinology and Metabolic Diseases[2], Dept. of Internal Medicine and Cardiology[3], Leiden University Medical Center, Leiden, The Netherlands

17.30 Einde programma in deze zaal.

Congresborrel, aansluitend diner in de Genderzaal.

Nederlandse Vereniging voor Hepatologie (klinische voordrachten) **Parkzaal**

12.30 Ontvangst, inschrijving, koffie

Voorzitters: B. van Hoek en C.M.J. van Nieuwkerk

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

13.00 Peginterferon alfa-2b alone or in combination with lamivudine for chronic HBeAg-positive Hepatitis B: a randomized controlled trial. *(p.59)*
H.L.A. Janssen, M. van Zonneveld, H. Senturk, S. Zeuzem, U. Akarca, Y. Cakaloglu, K. Simon, T. So Man Kit, G. Gerken, R.A. de Man, H.G.M. Niesters, S.W. Schalm for the HBV 99-01 Study Group. Dept of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, The Netherlands

13.10 Abnormal hepatocystin caused by truncating PRKCSH mutations lead to autosomal dominant polycystic liver disease. *(p 60)*
J.P.H. Drenth[1,2] , Esa Tahvanainen[3], R.H.M. te Morsche[1], P. Tahvanainen[4], H. Kääriäinen[5] K. Höckerstedt[6], J.M. van de Kamp[7], M.H. Breuning[7], J.B.M.J. Jansen[1]. Dept of Medicine, Div of Gastroenterology and Hepatology[1], University Medical Center St. Radboud, Nijmegen, The Netherlands and Cell Biology and Metabolism Branch[2], National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, USA, Dept of Medical Genetics[3], University of Helsinki, Helsinki, Finland, Dept of Human Molecular Genetics[4], National Public Health Institute, Helsinki, Finland, Dept of Medical Genetics, University of Turku, and Dept of Pediatrics[5], Turku University Central Hospital, Turku Finland, Transplantation and Liver Surgery Unit[6], Helsinki University Hospital, Helsinki, Finland, Dept of Human and Clinical Genetics[7], Leiden University Medical Center, Leiden, The Netherlands

13.20 Viral dynamics during a 24-weeks course of tenofovir in patients with lamivudine-resistant hepatitis B virus mutants. *(p.61)*
A.A. van der Eijk[1], B.E. Hansen[2], H.G.M. Niesters[3], H.L.A. Janssen[1], M.E. van de Ende[4], S.W. Schalm[1], R. A. de Man[1]. Dept of Gastroenterology & Hepatology[1], Epidemiology & Biostatistics[2], Virology[3] and Internal Medicine[4], Erasmus MC Rotterdam, the Netherlands

13.30 Viral dynamics during PEG-interferon alone and in combination with lamivudine. *(p.62)*
M. van Zonneveld[1], B.E. Hansen[2], H.G.M. Niesters[3], R.A. de Man[1], S.W. Schalm[1], H.L.A. Janssen[1]. Depts of Gastroenterology and Hepatology[1], Epidemiology and Biostatistics[2] and Virology[3], Erasmus MC, Rotterdam, The Netherlands

13.40 Improved results of resection of hilar cholangiocarcinoma (Klatskin tumors): A single-center, 15-year experience. *(p.63)*
S. Dinant[1], M.F. Gerhards[2], O.R.C. Busch[1], H. Obertop[1], D.J. Gouma[1], T.M. van Gulik[1]. Dept. of surgery, Academic Medical Center[1], Onze Lieve Vrouwe Gasthuis[2], Amsterdam

13.50 Exacerbation of chronic hepatitis B in relation to genotype and response of treatment with pegylated interferon alone or its combination with lamivudine. *(p.64)*
H.J. Flink[1], M. van Zonneveld[1], H.G.M. Niesters[2], R.A. de Man[1], S.W. Schalm[1], H.L.A. Janssen[1]. Dept of Gastroenterology & Hepatology[1], Virology[2], Erasmus MC, Rotterdam, The Netherlands

14.00 Liver histology in chronic hepatitis B patients after 1 year of treatment with pegylated interferon alpha-2b in combination with lamivudine or placebo. *(p.65)*
M. van Zonneveld[1], P. Zondervan[2], R.A. de Man[1], S.W. Schalm[1], H.L.A. Janssen[1]. Depts of Gastroenterology and Hepatology[1] and Pathology[2], Erasmus MC, Rotterdam, The Netherlands

14.10 Balancing Benefit and Burden in chronic hepatitis C: Recommendations on treatment continuation based on transaminase-levels and cost-per-cure. *(p.66)*
B.J. Veldt[1], B.E. Hansen[1,2], R.M.J. Eijkemans[3], R.J. de Knegt[1], T. Stijnen[2], S.W. Schalm[1], Dept of Gastroenterology and Hepatology[1], Epidemiology and Biostatistics[2], Public Health[3], Erasmus MC, University Medical Center Rotterdam, The Netherlands

14.20 Management of spontaneuous hemorrhage and rupture of hepatocellular adenomas. Is it time for a change? *(p.67)*
D. Erdogan, O. Busch, D.J. Gouma, T.M. van Gulik. Dept. of Surgery, Academic Medical Center, University of Amsterdam, The Netherlands

14.30 Circulating numbers of CD1d-restricted Natural Killer T cells in hepatitis C virus infected patients . *(p.68)*
H.J. van der Vliet[1], J.W. Molling[2], B.M. von Blomberg[2], C.J. Mulder[1], H.L. Janssen[3], N. Nishi[4], A.J. van den Eertwegh[5], R.J. Scheper[2] and C.M. van Nieuwkerk[1]. Depts of Gastroenterology[1], Pathology[2], and Oncology[5], Vrije Universiteit Medical Center, Amsterdam, The Netherlands; Dept of Gastroenterology, Erasmus Medical Center, Rotterdam[3]; Kirin Pharmaceutical Company, Kirin Brewery Co., Ltd., Gunma, Japan[4]

14.40 Early complications of radiofrequency ablation of liver tumours in the Netherlands. *(p.69)*
M.C. Jansen[1], F.H. van Duijnhoven[2], B. Fioole[3], R. van Hillegersberg[3], A.M. Rijken[4], F. van Coevorden[5], J.R. van der Sijp[6], R.A.E.M. Tollenaar[2], I.H. Borel Rinkes[3], J.M. Klaase[7], G. Slooter[8], T.M. van Gulik[1]. Dept of Surgery[1], AMC, Amsterdam, Dept of Surgery[2], LUMC, Leiden, Dept of Surgery[3], UMC, Utrecht, Dept of Surgery[4], Amphia hospital, Breda, Dept of Surgery[5], AvL, Amsterdam, Dept of Surgery[6], VUMC, Amsterdam, Dept of Surgery[7], MST, Enschede, Dept of Surgery[8], MMC, Eindhoven, The Netherlands

14.50 Health Related Quality of Life of Chronic Liver Patients; A Survey in Dutch patients. *(p 70)*
S.M. van der Plas[1], B.E. Hansen[1,2], J.B. de Boer[3], Th. Stijnen[2], J. Passchier[3], R.A. de Man[1], S.W. Schalm[1]. Depts of Gastroenterology and Hepatology[1], Epidemiology and Biostatistics[2], Medical Psychology and Psychotherapy[3] Erasmus MC, Rotterdam, The Netherlands

15.00 Theepauze

Nederlandse Vereniging voor Hepatologie (basale voordrachten) **Parkzaal**

Voorzitters: L. Klomp en J. Kwekkeboom

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

15.30 Regulatory T cells play a role in the persistence of hepatitis B virus infection. *(p.71)*
J.N. Stoop[1], R.G. van der Molen[1], L.J.W. van der Laan[2], E.J. Kuipers[1], Solko W. Schalm[1], J.G. Kusters[1], H.L.A. Janssen[1]. Dept of Gastroenterology and Hepatology[1] and Dept of Surgery[2], Erasmus MC, Rotterdam, The Netherlands

15.40 ApoAV expression reduces plasma triglycerides in mice by reducing VLDL-triglyceride production and by stimulating lipoprotein lipase-mediated VLDL-triglyceride hydrolysis. *(p.72)*
F.G. Schaap[1], P.C.N. Rensen[2,3], P.J. Voshol[2,4], H.N. van der Vliet[1], R.A.F.M. Chamuleau[1], L.M. Havekes[2,4,5], A.K. Groen[1], K. Willems van Dijk[4,6]. AMC Liver Center[1], Amsterdam, TNO-Prevention and Health[2], Gaubius Laboratory, Leiden, Depts of General Internal Medicine[3], Endocrinology[4], Cardiology[5] and Human Genetics[6], Leiden University Medical Center, The Netherlands

15.50 Differential effects of pharmacological LXR activation on peripheral and hepatic insulin sensitivity in lean and ob/ob mice. *(p.73)*
A. Grefhorst[1], T.H. van Dijk[1], A. Hammer[1], R. Havinga[1], P.H. Groot[2], D.-J. Reijngoud[1], F. Kuipers[1]. Lab of Pediatrics[1], University Hospital Groningen, Groningen, GlaxoSmithKline Pharmaceuticals[2], Stevenage, UK

16.00 In vivo binding of transcription factors to the carbamoylphosphate-synthetase (CPS) glucocorticoid-response unit. *(p.74)*
M. Hoogenkamp, I. C. Gaemers, W.H. Lamers. AMC Liver Centre, University of Amsterdam, The Netherlands

16.10 HNF4a binds Glutamine Synthetase upstream enhancer. *(p.75)*
V. Stanulovic, M. de Julio, T.B.M. Hakvoort and W.H. Lamers. AMC Liver Center, University of Amsterdam, The Netherlands

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Nederlandse Vereniging voor Hepatologie **Parkzaal**

Symposium on Hepatocellular Carcinoma

Chairmen: B. van Hoek en J.R.M. van der Sijp

16.20 Hormonal, chemotherapeutic and other systemic therapies
C. van Groeningen

16.40 Resection and Liver transplantation
R.J. Porte

17.10 Local ablation therapies
A.K. Burroughs, Royal Free Hampstead, London, UK

Pro/contra liver transplantation for HCC

17.40 Wider criteria for liver transplantation in HCC should be applied
J.N.M. IJzermans

17.50 Liver transplantation for HCC should be restricted or not done at all
A.K. Burroughs

18.00 Rebuttal, J.N.M. IJzermans

18.05 Rebuttal, A.K. Burroughs

18.10 Einde programma in deze zaal.

Diner.

Presidential Selection - plenaire sessie **Brabantzaal**

Voorzitter: J.B.M.J. Jansen

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

20.00 Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal origin. *(p.76)*
V.J. Verwaal[1], S. van Ruth[1], E. de Bree[1], H. van Tinteren[2], H. Boot[3], G.W. van Slooten[1], F.A.N. Zoetmulder[1]. Dept. of Surgery[1], Dept. of Medical Statistics[2] and Dept. of Gastroenterology[3], Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands

20.15 Small gallbladders stones, good gallbladder motility and fast crystallization are major risk factors for acute pancreatitis. *(p.77)*
N.G. Venneman[1], W. Renooij[1], P.M.N.Y.H. Go[2], I.A.M.J. Broeders[1], G.P. van Berge-Henegouwen[1], K.J. van Erpecum[1]. Depts of Gastroenterology and Surgery[1] Gastrointestinal Research Unit, University Medical Center Utrecht and Dept. of Surgery[2], St. Antonius Hospital, Nieuwegein, The Netherlands

20.30 Peptic ulcer bleeding, NSAID use and Helicobacter pylori infection; a prospective study evaluating incidence, prevalence and outcome. *(p.78)*
D. Ramsoekh[1], M.E. van Leerdam[1], E.A.J. Rauws[1], A.A.M. Geraedts[2], G.N.J. Tytgat[1]. Dept of Gastroenterology, Academic Medical Center[1], Onze Lieve Vrouwe Gasthuis[2], Amsterdam, The Netherlands

20.45 Molecular Aberrations are Still Present after Ablative Therapy of Barrett's Esophagus. *(p.79)*
M. Hage[1,2], H. van Dekken[2], K.J. Vissers[2], J. Haringsma[1], E.J. Kuipers[1], P.D. Siersema[1]. Depts. of Gastroenterology & Hepatology[1] and Pathology[2], Erasmus MC, Rotterdam, The Netherlands

21.00 **Altana lecture**
verzorgd door Prof. dr. G. van Asche, Leuven, België
Chronische anemie.

21.30 Ledenvergadering Nederlandse Vereniging voor Gastroenterologie

22.00 Voor alle congresdeelnemers: borrel in recreatievleugel ‘De Dommelpoort’, aangeboden en gesponsord door AstraZeneca.

Vrijdag 19 maart 2004

Casuïstiek voor de Klinikus **Brabantzaal**

Voorzitter: W. Hameeteman

8.00 Patiëntenbespreking

9.00 Einde programma

Sectie Gastrointestinale Endoscopie **Brabantzaal**

Voorzitter: Dr. W. Hameeteman

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

09.00 Narrow-band Imaging (NBI) in Barrett Esophagus (BE): What Features Are Relevant for The Detection of High-grade Dysplasia (HGD) and Early Cancer (EC)? *(p.80)*
M. Kara[1], M. Ennahachi[1], P. Fockens[1], F. Peters[1], F. ten Kate[2], J. Bergman[1]. Depts of Gastroenterology and Hepatology[1] and Pathology[2], Academic Medical Center, Amsterdam, The Netherlands

09.10 The First Experience with Video Autofluorescence Endoscopy (AFE) for The Detection of High Grade Dysplasia and Early Cancer (HGD/EC) in Barrett Esophagus (BE). *(p.81)*
M. Kara[1], P. Fockens[1], F. Peters[1], F. ten Kate[2], S. van Deventer[1], J. Bergman[1]. Depts of Gastroenterology and Hepatology[1] and Pathology[2], Academic Medical Center, Amsterdam, The Netherlands

09.20 Clinical implications of videocapsule endoscopy; 1-year follow-up. *(p.82)*
S.A.C. van Tuyl[1], M.F.J. Stolk[1], R. Timmer[1], E.J. Kuipers[2].Depts. of Gastroenterology[1], St. Antonius Hospital Nieuwegein and Erasmus University Medical Center Rotterdam[2], The Netherlands

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Nederlandse Vereniging voor Gastroenterologie **Brabantzaal**

09.30 **Frieda den Hartog Jager Lecture**
De Frieda den Hartog Jager lecture wordt dit maal verzorgd door Prof. dr. R. Fodde, Afdeling Pathologie, Erasmus MC Rotterdam:

'Stamcellen, signaaltransductie, genetische instabiliteit en darmkanker: it's all in the game'

10.00 Koffiepauze

Sectie Gastrointestinale Endoscopie **Brabantzaal**

Symposium Endo-echografie in Nederland. Hoe, bij wie en door wie?

Voorzitters: H. van Dullemen en R. Timmer

10.30 Opening en voorwoord.
H.M. van Dullemen, maag-darm-leverarts, Academisch Ziekenhuis Groningen

10.35 EUS; Materialen en training.
R. Timmer. maag-darm-leverarts, St. Antonius Ziekenhuis, Nieuwegein

11.00 EUS; Indicaties 2004.
P. Fockens, maag-darm-leverarts, Academisch Medisch Centrum, Amsterdam

11.30 EUS-FNA bij longziekten.
J. Annema, longarts, Leids Universitair Medisch Centrum.

11.55 Afsluiting

12.00 Lunchbuffet in expositehal

Nederlandse Vereniging voor Gastroenterologie **Baroniezaal**

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

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

08.30 MnSOD gene polymorphism predisposes to the development of gastroesophageal reflux disease. *(p.83)*
L.M.G. Moons[1], P.D. Siersema[1], J. van Delft[2], E.J. Kuipers[1], A.M. Knaapen[2], Han Geldof[3], W.A. Bode[3], R.W.H. Gottschalk[2], A.H.M. van Vliet[1], J.C.S. Kleinjans[2], J.G. Kusters[1]. Dept of Gastroenterology and Hepatology[1], Erasmus MC, Rotterdam, Dept of Health Risk Analysis and Toxicology[2], University of Maastricht, Dept of Gastroenterology and Hepatology[3], IJsselland Hospital, Capelle aan den IJssel, The Netherlands

08.40 Long mucin 6 alleles are associated with increased susceptibility to Helicobacter pylori infection. *(p.84)* M.J.R. Janssen, P. Gritters, R.H.M. Te Morsche, J.P.H. Drenth, R.J.F. Laheij & J.B.M.J. Jansen. Dept of Gastroenterology & Hepatology, University Medical Center St. Radboud, Nijmegen, The Netherlands

08.50 Host factors, IL1B-511 & IL-1RN gene polymorphisms, and bacterial factors of Helicobacter pylori, cagA and vacA subtypes, in peptic ulcer disease and non ulcer dyspepsia: a synergistic effect. *(p.85)* S. Ouburg[1], A. van der Ende[2], J.B.A. Crusius[1], Y. Pannekoek[2], R.W.M. van der Hulst[3], A. Salvador Peña[1], S.A. Morré[1]. Lab of Immunogenetics [1] Vrije Universiteit Medical Center, Amsterdam, Dept of Medical Microbiology[2], Academic Medical Center, Amsterdam, Dept of Gastroenterology[3], Kennemer Gasthuis, Loc. Johannes de Deo, Haarlem, The Netherlands

09.00 Molecular Characterization of Hepatocystin, the Protein that is Defective in Autosomal Dominant Polycystic Liver Disease. *(p.86)*
J.P.H. Drenth[1,2] J.A. Martina[1], R.H.M. te Morsche[2], J.B.M.J. Jansen[2], J.S. Bonifacino[1]. From Cell Biology and Metabolism Branch, National Institute of Child Health and Human Development, National Institutes of Health[1] ,Bethesda, USA and Dept of Medicine, Div of Gastroenterology and Hepatology[2] , University Medical Center St. Radboud, Nijmegen, The Netherlands

09.10 Non-absorbable fat enhances the fecal excretion of 2,2',4,4'-tetrabromodiphenyl ether (BDE-47) in rats by interruption of its enterohepatic circulation *****. *(p.87)*
L. Meijer[1], A.M. Hafkamp[1], W.E. Bosman[1], R. Havinga[1], A. Bergman[2], P.J.J. Sauer[1], H.J. Verkade[1]. Pediatric Gastroenterology / Research Lab Pediatrics[1], University Hospital, Groningen, The Netherlands; Dept. Environmental Chemistry[2], Stockholm University, Sweden

09.20 NOD2 mediates anti-inflammatory signals induced by TLR2 ligands: implications for Crohn's disease. *(p.88)*
D. de Jong[1], M.G. Netea[2,4], B.J. Kullberg[2,4], B. Franke[3], T. Sprong[2,4], T.H.J. Naber[1], J.P.H. Drenth[1], and J.W.M. Van der Meer[2,4]. Depts of Gastroenterology[1], Medicine[2], and Human Genetics[3], University Medical Center St. Radboud Nijmegen, and Nijmegen University Center of Infectious Diseases[4], Nijmegen, The Netherlands

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Sectie Experimentele Gastroenterologie **Baroniezaal**

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

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

09.30 IFN-γ mediated epithelial barrier disruption involves claudin-2 cleavage. *(p.89)*
L.E.M. Willemsen[1], P.J. Hoetjes[1], S.J.H. van Deventer[2], E.A.F. van Tol[1]. Numico Research BV[1], Wageningen, Exp. Internal Medicine[2], AMC, Amsterdam, The Netherlands

09.40 The presence of the cag Pathogenicity Island is associated with increased ros scavenging by helicobacter pylori. *(p.90)*
J.G.Kusters[1], R.G.J. Pot[1], J.J. Briede[2], E.J. Kuipers[1], A.H.M. van Vliet[1], J.C.S. Kleinjans[2]. Dept of Gastroenterology and Hepatology[1], Erasmus MC, University medical centre Rotterdam, Dept of Health Risk Analysis and Toxicology[2], Faculty of Health Sciences, University of Maastricht, Maastricht, The Netherlands

09.50 Analysis of Functional Interleukin-12 Gene Polymorphisms in the Susceptibility to Crohn's Disease. *(p.91)*
A. Zwiers[1], D. Seegers[1], R. Heijmans[1], A. Koch[2], J. Hampe[2], A.S. Peña[1], S. Schreiber[2] and G. Bouma[1]. Lab of Immunogenetics[1], Vrije Universiteit Medical Center, Amsterdam, the Netherlands and Klinik fur Allgemeine Innere Medizin, Christian-Albrechts-Universitat Kiel [2] , Germany

10.00 Koffiepauze

Voorzitters: G. Dijkstra en J.G. Kusters

10.30 The rotavirus enterotoxin NSP4 interacts with intestinal basement membrane proteins *****. *(p.92)* S. Einerhand, J. Boshuizen, J. Rossen, C. Sitaram, F. Kimenai, Y. Simons-Oosterhuis, C. Laffeber, H. Büller. Lab. of Pediatrics, Erasmus MC / Sophia Children's Hospital, Rotterdam, the Netherlands

10.40 Inhibition of JNK MAPK activity improves epithelial barrier integrity. *(p.93)*
L.E.M. Willemsen[1], T. Wijnhoven[1], S.J.H. van Deventer[2], E.A.F. van Tol[1]. Numico Research B.V.[1], Wageningen, Dept. of Exp. Internal Medicine[2], Academic Medical Center, Amsterdam, The Netherlands

10.50 Multidrug Resistance Protein (MDR1) is decreased in inflamed intestinal epithelium in inflammatory bowel disease. *(p.94)*
H. Blokzijl[1], S. Vander Borght[2], L. Libbrecht[2], L.I.H. Bok[1], G. Dijkstra[1], H. Moshage[1], K.N. Faber[1], T.A.D. Roskams[2], P.L.M. Jansen[3]. Dept. of Gastroenterology and Hepatology[1], University Hospital Groningen, The Netherlands, Lab of Morphology and Molecular Pathology[2], University of Leuven, Leuven, Belgium; Dept. of Gastroenterology and Hepatology[3], Academic Medical Center, Amsterdam, The Netherlands

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Sectie Experimentele Gastroenterologie **Baroniezaal**

International Teaching Session 'Of Milk and Man'

Voorzitters: G. Dijkstra en J.G. Kusters

11.00 Lactose intolerance in the Netherlands: fact or fiction?
H.A. Koetse, Pediatrician, University Hospital Groningen

11.30 Expression and regulation of lactase in the intestine
R.K. Montgomery, Pediatrician, Children's Hospital, Harvard University, Boston, U.S.A.

12.00 Lunchbuffet in expositiehal

Sectie Neurogastroenterologie en Motiliteit **Auditorium**

Voorzitter: G.E.E. Boeckxstaens en A.A.M. Masclee

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

08.30 Air swallowing, intragastric air and gaseous and liquid gastroesophageal reflux: a study using multiple intraluminal impedance. *(p.95+96)*
A.J. Bredenoord[1], B.L. Weusten[1], R. Timmer[1], L.M. Akkermans[2] and A.J. Smout[2]. Dept of Gastroenterology[1], St Antonius Hospital, Nieuwegein and Gastrointestinal Research Unit[2], University Medical Center Utrecht, the Netherlands

08.40 Increased oesophagogastric junction (OGJ) bolus transit time is related to postfundoplication dysphagia. *(p.97)*
R.C.H. Scheffer[1], M. Samsom[1], A. Haverkamp[1], J. Oors[1], G.S. Hebbard[2], H.G. Gooszen[1]. Gastrointestinal Research Unit, Depts of Gastroenterology and Surgery[1], University Medical Center, Utrecht, The Netherlands and Div of Gastroenterology, Medical Dept[2], Melbourne University, Australia

08.50 Endoscopic Anti-reflux Therapy: Effect of Radiofrequency Energy Therapy on Reflux Mechanisms and Vagus Nerve Function. *(p.98)*
J. Haringsma[1], A.A.M. Masclee[2], C. de Jong[2], E.J. Kuipers[1]. Depts. Gastroenterology and Hepatology[1], Erasmus MC University Medical Center Rotterdam, and Leiden University Medical Center[2], The Netherlands

09.00 The relationship between gastric volumes and dyspeptic symptoms assessed by SPECT scanning after the drink test in healthy volunteers. *(p.99)*
B.D. van den Elzen[1], R.J. Bennink[2], R. Holman[3], G.N. Tytgat[1], G.E. Boeckxstaens[1]. Dept. of Gastroenterology[1], Nuclear Medicine[2] and Clinical Epidemiology and Biostatistics[3], Academic Medical Centre, Amsterdam, The Netherlands

09.10 Assessment of visceral sensitivity using radio telemetry in a rat model of maternal separation. *(p.100)*
O. Welting[1], R.M. van den Wijngaard[1], M. in 't Hout[1], M.J.M.A. Nijsen[2], W.J. de Jonge[1], G.E. Boeckxstaens[1]. Dept. of Gastroenterology and Hepatology[1], AMC, Amsterdam, The Netherlands. Johnson & Johnson Pharmaceutical Research and Development[2], Beerse, Belgium

09.20 Rectal compliance is disturbed in children with severe constipation*. *(p.101)*
W.P. Voskuijl[1], M.A. Benninga[1], R. van Ginkel[1], G.A. Hart[2], J.A.J.M. Taminiau[1], and G.E. Boeckxstaens[3]. Dept of Pediatric Gastroenterology and Nutrition[1], Emma Children's Hospital, Dept of Biostatistics[2], Dept of Gastroenterology[3], Academic Medical Center, Amsterdam, the Netherlands

09.30 A scoring method on plain abdominal x-rays in the diagnosis of childhood constipation revisited *. *(p.102)*
F. de Lorijn[1], J. Heijmans[1], R. van Rijn[2], J.A.J.M. Taminiau[1], M.A. Benninga[1]. Dept of Paediatric Gastroenterology and Nutrition[1], Emma Children's Hospital, Dept of Radiology[2], Academic Medical Centre, Amsterdam, The Netherlands

09.40 Diurnal Pattern and Reproducibility of Colonic Motility during Ambulatory Recording. *(p.103)*
E.A. van Hoboken, M. Yuksel, A.A.M. Masclee, Department of Gastroenterology-Hepatology, Leiden University Medical Center, Leiden, The Netherlands

09.50 Tumor necrosis factor-alpha and interleukin 10 gene polymorphisms in Irritable Bowel Syndrome. *(p.104)*
P.P.J. van der Veek, Y.E. de Kroon , M. van den Berg, H.W. Verspaget, A.A.M. Masclee. Dept of Gastroenterology and Hepatology, Leiden University Medical Center, The Netherlands

10.00 Koffiepauze

Nederlandse Vereniging voor Gastroenterologie **Auditorium**

Voorzitters: H. Escher en E.C. Klinkenberg-Knol

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

10.30 Gastric acid-suppressive drugs and the risk of community-acquired pneumonia. *(p.105)*
R.J.F. Laheij[1], M.C.J.M. Sturkenboom[2,3], R-J. Hassing[2], J. Dieleman[2], B.H.C. Stricker[2,3], J.B.M.J. Jansen[1]. Dept of Gastroenterology[1], UMC St. Radboud, Nijmegen, Medical Informatics[2] and Epidemiology & Biostatistics[3], Erasmus Medical Center, Rotterdam, The Netherlands

10.40 Influence of pretreatment with a proton pump inhibitor (PPI) on Helicobacter pylori eradication: a meta-analysis. *(p.106)*
M.J.R. Janssen[1], R.J.F. Laheij[1], W.A. de Boer[1,2] & Jan B.M.J. Jansen[1]. Dept of Gastroenterology and Hepatology[1], University Medical Center St. Radboud, Nijmegen, Dept of Internal Medicine[2], Bernhoven Hospital, Oss, The Netherlands

10.50 Esophageal function after correction of esophageal atresia: follow-up after more than eighteen years *****. *(p.107)*
J.A. Deurloo[1], E.C.Klinkenberg[2], S.Ekkelkamp[1], D.C.Aronson[1]. Pediatric Surgical Center of Amsterdam[1],Emma Children's Hospital/AMC and Vrije Universiteit Medical Center, Dept of Gastroenterology[2], Vrije Universiteit Medical Center, Amsterdam, The Netherlands

11.00 Relationship between Upper Gastrointestinal Symptoms and Partial Gastric Volumes Measured by 3-Dimensional Ultrasonography. *(p.108)*
N. van Lelyveld , R.C.H. Scheffer, M.W. Mundt and M. Samsom. Gastrointestinal Research Unit, Depts of Gastroenterology and Surgery, University Medical Centre Utrecht, The Netherlands

11.10 Colorectal motor and sensory function in constipated and non-constipated patients after hysterectomy. *(p.109)*
P.P.J. van der Veek[1], F.G.M. Timmermans[1], P.T.M. Weijenborg[2] and A.A.M. Masclee[1]. Depts of Gastroenterology and Hepatology[1] and Gynecology[2], Leiden University Medical Center, Leiden, The Netherlands

11.20 Rectal function in functional non-retentive fecal soiling (fnrfs) *****. *(p.110)*
W.P. Voskuijl[1], M.A. Benninga[1], R. van Ginkel[1], G.A. Hart[2], J.A.J.M. Taminiau[1] and G.E. Boeckxstaens[3]. Dept of Pediatric Gastroenterology and Nutrition[1], Emma Children's Hospital, Dept of Biostatistics[2], Dept of Gastroenterology[3], Academic Medical Center, Amsterdam, The Netherlands

11.30 Follow-up of children with unrecognised coeliac disease (CD) identified after mass screening *****. *(p.111)*
M.L. Mearin[1], A.M. van Geel[2], C.G.D.S. Csizmadia[2], H.M. Koopman[2], H.B. Hylkema[2], J.J. Schweizer[1], S P Verloove-Vanhorick[3]. Dept. Paediatrics Leiden University Medical Centre[2] and Free University Medical Centre Amsterdam[1], TNO Prevention and Health Leiden[3], The Netherlands

11.40 Gene expression and mapping of nutrient regulated biological pathways in the human small intestine. *(p.112)*
F.J. Troost, R-J.M. Brummer. Nutrition and Toxicology Research Institute, Maastricht University, Maastricht, The Netherlands

11.50 Ghrelin and leptin levels in restrictive surgery, a 2 year follow-up study. *(p.113)*
J. Nijhuis[1], F.M.H. van Dielen[2], W.A. Buurman[1], J.W.M. Greve[2]. Dept. of General Surgery[1], Maastricht University and Dept. of General Surgery[2], University Hospital Maastricht, the Netherlands

12.00 Lunchbuffet in expositiehal

Sectie Gastrointestinale Endoscopie **Brabantzaal**

Voorzitter: W. Hameeteman en J.J.G.H.M. Bergman

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

13.30 Endoscopic Resection combined with Photodynamic Therapy for High Grade Dysplasia and Early Cancer in Barrett's Esophagus. *(p.114))*
F.P. Peters[1], M.A. Kara[1], W.D. Rosmolen[1], F.J.W. ten Kate[2], A.C. Bultje[3], K.K. Krishnadath[1], P. Fockens[1], J.J.B. van Lanschot[4], S.J.H. van Deventer[1], J.J.G.H.M. Bergman[1]. Depts of Gastroenterology[1], Pathology[2], Clinical Epidemiology and Biostatistics[3] and Surgery[4], Academic Medical Center, Amsterdam, The Netherlands.

13.40 Endoscopic Treatment of Barrett's neoplasia. *(p.115)*
J. Haringsma , P.D. Siersema, E.J. Kuipers. Dept. of Gastroenterology and Hepatology, Erasmus MC University Medical Center Rotterdam

13.50 Endosonographic staging of obstructive esophageal cancer: how far should we go? *(p.116)*
J.W. Poley[1], S. Darwish Murad[1], J. Haringsma[1], M.L. Hordijk[1], H.W. Tilanus[2], E.J. Kuipers[1].
Depts of Gastroenterology and Hepatology[1] and Surgery[2], Erasmus MC / University Medical Center Rotterdam, the Netherlands

14.00 Endoscopic screening for synchronous esophageal cancer in patients with head and neck cancer. *(p.117)*
H.Boot[1], M.A.Stam[2], A.J.M.Balm[2], M.W.M. van den Brekel[2], B.G.Taal[1], A.Cats[1]. Dept. of Gastroenterology[1] and Dept. of Otolaryngology and Head and Neck Surgery[2], Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands

14.10 The trucut biopsy needle in EUS: does it improve the diagnostic yield? Preliminary results of EUS-guided histological tissue sampling in 11 patients. *(p.118)*
G.H.A. Dodemont[1], B.L.A.M. Weusten[1], C.A. Seldenrijk[2], P.C. de Bruin[2], R. Timmer[1]. Depts of Gastroenterology[1] and Pathology[2], St Antonius Hospital, Nieuwegein, The Netherlands

14.20 What is the appropriate screening protocol in HNPCC?. *(p.119)*
A.E. de Jong[1,2], F.M. Nagengast[3], F.H. Menko[4], J.H. Kleibeuker[5], G. Griffioen[2], A. Cats[6], H.F.A. Vasen[1,2]. The Netherlands Foundation for the Detection of Hereditary Tumours[1], Dept. of Gastroenterology[2], Leiden University Medical Centre, Dept. of Gastroenterology[3], University Medical Centre St Radboud Nijmegen, Dept. of Human and Clinical Genetics[4], VU University Medical Centre Amsterdam, Dept. of Gastroenterology[5], University Hospital Groningen, Dept. of Gastroenterology[6], the Netherlands Cancer Institute Amsterdam

14.30 Value of serology in the diagnosis of advanced gastric body atrophy: a study in a Dutch primary community. *(p.120)*
A. Korstanje[1], S. van Eeden[2], G.J. Offerhaus[2], G. den Hartog[3], I. Biemond[4], C. Lamers[4]. General practice 's-Gravenpolder[1], Dept of Pathology[2], Academic Medical Centre, Amsterdam, Dept of Gastroenterology[3], Rijnstate Hospital Arnhem, Dept of Gastroenterology[4], Leiden University Medical Centre, The Netherlands

14.40 Barrett's Esophagus after Pneumo-dilation for Achalasia. *(p.121)*
P. Scholten[1], T.J. Caljé[1], R.J. Vaessen[1], G.L.Ong[2], P.D. Siersema[1], J.Haringsma[1], E.J. Kuipers[1]. Depts of Gastroenterology and Hepatology[1], and Surgery[2], Erasmus MC University Medical Center, Rotterdam, The Netherlands

14.50 Esophagitis is very common in patients with achalasia after treatment with pneumatic dilatation. *(p.122)*
I. Leeuwenburgh[1], H.van Dekken[2], P. Scholten[1], J. Haringsma[1], P.D. Siersema[1] , E.J. Kuipers[1]. Dept of Gastro-enterology and Hepatology[1] and Dept of Pathology[2], Erasmus University Medical Center Rotterdam, The Netherlands

15.00 Koffie/thee, einde programma

Sectie Experimentele Gastroenterologie **Baroniezaal**

Voorzitters: M.A.C. Meijssen en A.W.C. Einerhand

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

13.30 In high-grade dysplasia in Barrett's esophagus MUC4 is increased and is associated with a pro-apoptotic Bax/Bcl-2 ratio. *(p.123)*
D.A. Bax[1], J. Haringsma[1], P.D. Siersema[1], P. Blok[2], H. van Dekken[3], A.W.C. Einerhand[4], E.J. Kuipers[1], J.G. Kusters[1]. Depts of Gastroenterology and Hepatology[1] and Pathology[3], ErasmusMC - University Medical Center Rotterdam, Laboratory of Pediatrics[4] ErasmusMC - Sophia Children's Hospital Rotterdam and Dept. of Pathology[2] Leyenburg Ziekenhuis Den Haag

13.40 The role of the Helicobacter pylori outer membrane proteins AlpA and AlpB in the colonization of the guinea pig stomach. *(p.124)*
R. de Jonge[1], A.H.M. van Vliet[1], Z. Durrani[2], S.G. Rijpkema[2], E.J. Kuipers[1], J.G. Kusters[1]. Dept of Gastroenterology and Hepatology[1], Erasmus MC, Rotterdam, The Netherlands, Div of Bacteriology[2], National Institute for Biological Standards and Control, Potters Bar, United Kingdom

13.50 Polymorphism in the Interleukin 12B Gene in Colitis Susceptible Mice Affects Formation of Biologically Active IL-12 heterodimers. *(p.125)*
A. Zwiers[1], T. Konijn[1], M.E.A. Borm[1], A.S. Peña[1], W. Strober[1,2] and G. Bouma[1,2]. Lab of Immunogenetics[1], Vrije Universiteit Medical Center, Amsterdam, the Netherlands and the Mucosal Immunity Section[2], National Institutes of Health, Bethesda, MD, USA

14.00 The cholinergic anti-inflammatory pathway mediates the severity of experimental acute pancreatitis in mice. *(p.126)*
D.J. van Westerloo[1], M.J. Bruno[2], S. Florquin[3], K.J. Tracey[4], A.F. de Vos[1] and T. van der Poll[1]. Depts of Experimental Internal Medicine[1], Gastroenterology[2] and Pathology[3] at the Academic Medical Center, Amsterdam, the Netherlands and the Lab of Biomedical Science[4], North Shore Long Island Jewish Research Institute, New York, USA.

14.10 Effect of gene promoter polymorphisms on mucosal TNF-α and matrix metallo-proteinase-2 and -9 protein production in patients with inflammatory bowel disease. *(p.127)*
M.J.W. Meijer, M.A.C. Mieremet-Ooms, R.A. van Hogezand, C.B.H.W. Lamers, H.W. Verspaget. Dept of Gastroenterology-Hepatology, Leiden University Medical Center, Leiden, The Netherlands

14.20 Conjugated but not Unconjugated Bile Acids Induce Time-Dependent Increases in Proliferation in Barrett's Esophagus Ex Vivo Cultures. *(p.128)*
P.D. Siersema[1], B.S. Kaur[2], D.M. Toivola[2], A.F. Hofmann[3], M.B. Omary[2], E.J. Kuipers[1], G. Triadafilopoulos[2]. Dept of Gastroenterology & Hepatology [1] , Erasmus MC, Rotterdam, The Netherlands, Div. of Gastroenterology and Hepatology[2] , Stanford University, Palo Alto, CA, USA, Div. of Gastroenterology and Hepatology[3] , University of California, San Diego, CA, USA

14.30 The NikR regulatory protein governs transcriptional regulation of NixA-mediated nickel-uptake in Helicobacter pylori. *(p.129)*
F.D. Ernst[1], E.L. Benanti[2], E.J. Kuipers[1], A. Heijens[1], J. Stoof[1], J.G. Kusters[1], P.T. Chivers[2], A.H.M. van Vliet[1]. Dept of Gastroenterology and Hepatology[1], Erasmus MC-University Medical Center Rotterdam, The Netherlands. Dept of Biochemistry and Molecular Biophysics[2], Washington University School of Medicine, St. Louis, MO, USA

14.40 Protective effect of exogenous alkaline phosphatase in the inflammatory response in secondary peritonitis. *(p.130)*
S.Q. van Veen[1], A.K. van Vliet[1], M.A. Boermeester[2], M Wulferink[3], T.M. van Gulik[1]. Surgical Lab[1] and Dept of Surgery[2], Academical Medical Center, Amsterdam, AM-Pharma[3], Bunnik, The Netherlands

14.50 Microarray analysis implicates calprotectin as potential novel tumor marker for high-grade dysplasia in Barrett's esophagus. *(p.131)*
D.A. Bax[1], J. Haringsma[1], H. van Dekken[2], P.D. Siersema[1], J.G. Kusters[1], E.J. Kuipers[1], Depts of Gastroenterology and Hepatology[1] and Pathology[2], ErasmusMC - University Medical Center Rotterdam, The Netherlands

15.00 Koffie/thee, einde programma

Nederlandse Vereniging voor Gastroenterologie **Auditorium**

Voorzitters: D.J. de Jong en P.D. Siersema

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

13.30 Quality of life after palliative treatment for esophageal carcinoma: a longitudinal prospective comparison between stent placement and single dose brachytherapy. *(p.132)*
M.Y.V. Homs[1], M.L. Essink-Bot[2], G.J.J.M. Borsboom[2], E.W. Steyerberg[2], P.D. Siersema[1] for the Dutch SIREC study group. Dept. of Gastroenterology & Hepatology[1] and Dept of Public Health[2], Erasmus MC / University Medical Center Rotterdam, the Netherlands

13.40 Clinical significance of immunohistochemically detected micrometastases in histologically negative lymph nodes of patients with adenocarcinoma of the distal oesophagus or gastric cardia. *(p.133)*
C.J. Buskens[1], P. Scheunemann[2], F.J.W. Ten Kate[3], S.B. Hosch[2], H. Obertop[1], J.R. Izbicki[2], J.J.B. van Lanschot[1]. Depts of Surgery[1] and Pathology[3], Academic Medical Center, Amsterdam, The Netherlands; and Dept of Surgery[2], University Hospital Eppendorf, Hamburg, Germany.

13.50 Colorectal Neoplasia in Veterans is Associated with Barrett's Esophagus but not with use of Proton-Pump Inhibitors (PPIs) or Aspirin/NSAIDs. *(p.134)*
P.D. Siersema[1], S. Yu[2], P. Sahbaie[2], E.W. Steyerberg[1], E.J. Kuipers[1], G. Triadafilopoulos[2]. Dept. of Gastroenterology & Hepatology[1], Erasmus MC, Rotterdam, The Netherlands and Div. of Gastroenterology and Hepatology[2], Stanford University, Palo Alto, CA, USA

14.00 Barrett's esophagus is associated with an increased epithelial inflammation. *(p.135)*
L.M.G. Moons[1], J.G. Kusters[1], E.J. Kuipers[1], W.M.W. Tra[1], H. van Dekken[2], A.H.M. van Vliet[1], P.D. Siersema[1]. Dept of Gastroenterology and Hepatology[1], Erasmus MC, Rotterdam, Dept of Pathology[2], Erasmus MC, Rotterdam, The Netherlands

14.10 Initial and Long-term Outcome of Biliary Bypass Surgery in Periampullary and Pancreatic Carcinoma. *(p.136)*
K.F.D. Kuhlmann, D. van Poll, S.M.M. de Castro, O.R.C. Busch, T.M. van Gulik, H. Obertop, D.J. Gouma. Dept of Surgery, Academic Medical Center of the University of Amsterdam, The Netherlands

14.20 Genetic polymorphisms in detoxification enzymes and colorectal cancer risk. *(p.137)*
E.M.J. van der Logt[1], S.M. Bergevoet[1], H.M.J. Roelofs[1], Z. van Hooijdonk[1], T. Wobbes[2], J.B. de Kok[3], F.M. Nagengast[1], W.H.M. Peters[1]. Depts of Gastroenterology[1], Surgery[2] and Clinical Chemistry[3], University Medical Centre St. Radboud, Nijmegen, The Netherlands

14.30 Concordance of serologic and genetic markers in twins with inflammatory bowel disease. *(p.138)*
S. Joossens[1], M. Romberg-Camps[2], S. Vermeire[1], K. de Boer[2], G. Claessens[1], M. Russel[3], M. Pierik[1], N. Van Schuerbeek[1], R. Vlietinck[4], X. Bossuyt[5], P. Rutgeerts[1]. Dept of Gastroenterology[1], University Hospital Gasthuisberg Leuven, Belgium, Dept of Gastroenterology[2], University Hospital Maastricht, the Netherlands, Dept of Gastroenterology[3], Medisch Spectrum Twente, Enschede, the Netherlands, Center of Epidimiology and Human Genetics[4], Catholic University Leuven, Belgium, Lab. Medicine, Immunology[5], University Hospital Gasthuisberg Leuven, Belgium

Vrijdag 19 maart 2004

14.40 TPMT polymorphisms in a Dutch population of inflammatory bowel disease patients. *(p.139)*
A.J. van Vuuren, C.J. van der Woude, J.S. Burgerhart, J.G. Kusters, E.J. Kuipers. Dept. of Gastroenterology & Hepatology, Erasmus University Medical Centre Rotterdam, the Netherlands

14.50 Segmental or radical colonic resection for Crohn's colitis? *(p.140)*
S.W. Polle[1], J.F.M. Slors[1], J.F.W.M. Bartelsman[2], D.J. Gouma[1], W.A. Bemelman[1]. Depts of Surgery[1] and Gastroenterology[2], Academic Medical Center, Amsterdam, the Netherlands

15.00 Koffie/thee, einde programma

Vereniging Maag Darm Lever Verpleegkundigen **Diezezaal**

09.30 Ontvangst en koffie

10.00 Algemene ledenvergadering VMDLV, onder het voorzittersschap van dhr. H. Welling.

10.20 Verschillende toegangswegen voor enterale voeding, indicatiestelling en methodiek.
Mw. W. Arjaans, voedingsverpleegkundige VUMC. Amsterdam

10.50 Verpleegkundige aspecten bij sondevoeding thuis.
Dhr. B. Akkermans, verpleegkundige Sorgente

11.10 Koffiepauze

11.30 Voorbereiding op endoscopisch onderzoek, keuze te over?
Mw. T. van der Meulen, verpleegkundige polikliniek maag-darm-leverziekten VUMC Amsterdam

11.50 Spoelen, drinken of slikken, Klaen Prep versus phosphoral, een verpleegkundig onderzoek
Mw. U.M. Kemble, Endoscopie verpleegkundige AMC Amsterdam.

12.10 Biofeedback training bij gestoorde functionaliteit van de bekkenbodem, een verpleegkundig aandachtsgebied.
Mw. J. Duncan, Biofeedback Nurse specialist St. Marks Hospital London

12.30 Lunchbuffet expositiehal

Sectie Endoscopie Verpleegkundigen en Assistenten **Diezezaal**

13.30	Verpleegkundige rol bij capsule endoscopie Mw. L. van Duin, endoscopieverpleegkundige LUMC Leiden
13.50	Endoscopische anti-refluxbehandeling: Enterix procedure. Dhr. M. Brendel, productspecialist BSCI
14.10	Ontwikkeling beroepsdeelprofiel endoscopieverpleegkundige Dhr. L. Boekholt, medewerker AVVV
14.30	Algemene ledenvergadering SEVA onder voorzitterschap van mw. M. de Pater
15.00	Koffie/thee, einde programma

Endotoxin-related complications after systemic hypotension are effectively reduced by a lipid-rich enteral nutrition in bile duct-ligated rats

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

Cholestatic patients are at risk for septic complications after major surgery due to an increased susceptibility to endotoxin and systemic hypotension. Thus far, no effective clinical therapy reduces postoperative compliations. Recently, we showed that high-fat enteral nutrition decreases endotoxin and inflammation after hemorrhagic shock. Since it is unknown whether an intact bile flow is required for this observed protection, we studied the effect of high-fat enteral nutrition on endotoxin, inflammation and gut barrier function in bile duct-ligated (BDL) rats with systemic hypotension.
BDL rats were fasted or fed with a low-fat or high-fat enteral nutrition before hemorrhagic shock. At 90 minutes, endotoxin and TNF-α were determined in plasma. Distribution of a tight junction protein, zonula occludens protein 1 (ZO-1) was assessed by immunofluorescence. Intestinal permeability to HRP was determined ex vivo in the ileum.
Plasma endotoxin decreased after hemorrhagic shock in BDL-rats fed with high-fat nutrition (15±3 pg/ml) compared to fasted (32±1 pg/ml, $p<0.001$) or low-fat treated rats (26±6 pg/ml, $p<0.01$). In line, plasma TNF-α was reduced in high-fat treated rats (61±20 pg/ml) compared to fasted (188±26 pg/ml, $p<0.05$) or low-fat treated rats (105±20, $p<0.01$). ZO-1 was diminished in ileum of non-treated rats, but remained unchanged in high-fat treated rats. The increased intestinal permeability to HRP in low-fat treated (2.4±0.3 µg/ml) and fasted BDL-rats (7.6±0.3 µg/ml) was also reduced by high-fat enteral nutrition (0.9±0.1 µg/ml, $p<0.001$ and $p<0.001$ respectively).
Conclusion: These results suggest that an intact bile flow is not required for the protective effect of high-fat enteral nutrition on hemorrhagic shock-induced endotoxemia, inflammation and gut barrier loss. Furthermore, high-fat enteral nutrition may be a new, simple and effective strategy to prevent endotoxin-mediated complications in cholestatic patients undergoing major surgery.

Subtotal Colectomy Does Not Reduce Pancreatic Infection in Experimental Acute Pancreatitis

L.P. van Minnen[1], V.B. Nieuwenhuijs[1], M.T. de Bruijn[1], M.R. Visser[2], L.M.A. Akkermans[1], H.G. Gooszen[1]. Depts of Surgery[1] and Microbiology[2], University Medical Center, Utrecht, The Netherlands

Subtotal colectomy prior to experimental acute pancreatitis (AP) in rats has been shown to reduce mortality. However, the effect of subtotal colectomy on proximal small bowel bacterial overgrowth and infection of pancreatic necrosis, is unknown. The aim of this experiment was to investigate these effects of subtotal colectomy in rats with acute pancreatitis.

50 male Sprague-Dawley rats were allocated in four study groups. All underwent two laparotomies, with a 14-day interval. Group I: sham laparotomy and saline biliary duct infusion, group II: subtotal colectomy and saline infusion, group III: sham laparotomy and induction of AP (ductal infusion of 10 mM glycodeoxycholic acid, followed by intravenous cerulein) and group IV: subtotal colectomy and AP. Seventy-two hours after second laparotomy blood, peritoneal fluid, mesenteric lymph nodes, liver, spleen, pancreas, duodenum and ileum were collected for microbiological analysis.

A total of 39 rats was included. Seven rats were excluded for hyperbilirubinaemia, four rats died during surgery. There was no mortality due to AP. Subtotal colectomy caused duodenal and ileal bacterial overgrowth with aerobes (group I vs II, duodenum ^{10}log CFU(colony forming units)/g = 4.25 vs 5.46, p=0.027; Ileum ^{10}log CFU/g = 5.06 vs 6.59, p=0.015). Total bacterial counts in the pancreas, duodenum and ileum of rats with AP and previous colectomy were significantly higher than in rats with AP only (group III vs IV: pancreas ^{10}log CFU/g = 4.30 vs 5.91, p=0.012; duodenum ^{10}log CFU/g = 5.52 vs 6.59, p=0.047; ileum ^{10}log CFU/g = 6.66 vs 7.64, p=0.049). Duodenal bacterial overgrowth and pancreatic infection with gram-positive aerobes correlated significantly (r = 0.78, p<0.01).

Conclusions: Duodenal bacterial overgrowth plays an important role in infection of pancreatic necrosis. Subtotal colectomy induces small bowel bacterial overgrowth, with increased pancreatic infection in acute pancreatitis.

Experienced problems and expected professional care in patients after surgery for esophageal cancer

E.M.L. Verschuur, T.C.K. Tran, E.J. Kuipers, H.W. Tilanus, P.D. Siersema. Dept of Gastroenterology and Hepatology, Erasmus MC, Rotterdam, The Netherlands

Surgery for esophageal cancer is a serious life-event, which significantly influences quality of life. It is insufficiently known which problems patients experience after surgery for esophageal cancer. Moreover, it is unclear whether patients expect professional care for these problems. Thirty patients (mean age: 62.3 yr; 21 males) filled in a questionnaire on experienced physical, psychological and social problems after a median of 6 (range: 3-12) months after esophageal surgery. Patients were interviewed afterwards to collect additional information. The experienced problems and the expected professional care were recorded. The association between dilations for anastomotic strictures and neo-adjuvant therapy, and experienced problems was analyzed. Patients most frequently recorded physical problems, i.e. early satiety [n=29 (99%)], eating problems [n=27 (90%)], fatigue [n=25 (84%)] and constipation/diarrhea [n=23 (77%)]. Although patients felt depressed at times [n=19 (63%)] and were afraid for metastases [n=24 (80%)], physical suffering [n=16 (53%)] or death [n=14 (47%)], these emotions did not predominate. Patients with 3 or more dilations experienced more often swallowing problems (p=0.027) and early satiety (p=0.035) than patients with fewer or no dilations. Patients who did not receive neo-adjuvant therapy (n=15) had more often the impression of 'lost body control' (p=0.025) and problems with decision-making (p=0.027). More than half of patients expected treatment and advice for physical problems. For psychosocial problems, the majority preferred support from family and friends.
Conclusions: Physical problems are frequently experienced after an operation for esophageal cancer for which patients expect professional care. Psychological and social problems are present but not predominant. It remains to be established whether this is due to the fact that sufficient support from family and friends is available, or that patients simply deny these problems.

Poor quality of life after colon interposition compared to gastric tube for esophageal cancer replacement.

H.A. Cense[1], M.R.M. Visser[2], A.G.E.M. de Boer[2], J.W. van Sandick[1], B.Lamme[1], H.Obertop[1], J.J.B. van Lanschot[1]. Depts of Surgery[1] and Medical Psychology[2], Academic Medical Center at the University of Amsterdam, The Netherlands

After esophagectomy for cancer a reconstruction by colon interposition can be performed when a gastric tube is not feasible. The aim of this study was to assess the quality of life in patients at least six months after esophageal cancer resection and colon interposition without signs of recurrent disease. The results were compared with previously published data of patients after esophageal cancer resection and gastric tube reconstruction.
Between January 1993 and January 2002, 38 patients underwent a colon interposition after esophagectomy. In march 2002 a Quality of Life assessment was carried out of the 14 patients who had survived at least half a year and were disease free. After an average follow-up of 35 months (7-97) the patients were visited at home and asked to fill in questionnaires which consisted of the Short Form-36 (SF-36) Health Survey to assess generic quality of life, an adapted Rotterdam Symptom Checklist to assess disease-specific quality of life and an additional questionnaire concerning other specific effects of the operation.
All patients returned the questionnaires. Compared to the patients with gastric tube reconstruction patients with a colon interposition scored significantly ($p < 0.05$) lower in five of the eight subscales of the SF-36 questionnaire: general health, physical role, vitality, social functioning and mental health. The most frequent symptoms as measured by the Rotterdam Symptoms Checklist were early satiety after a meal, dysphagia, fatigue, and loss of sexual interest. Six patients could not independently run their housekeeping and four patients still needed artificial oral nutrition.
Conclusion: Based on the SF-36 questionnaire patients after colon interposition have a poorer quality of life than patients after gastric tube reconstruction. Even long after the operation they have a broad spectrum of persisting symptoms. Prior to surgery these patients should be informed about the disabling long-term functional outcomes.

Five years results of the Manchet I trial: Randomised Controlled Trial of Laparoscopic versus Open Nissen Fundoplication

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The randomised clinical trial to compare laparoscopic (LNF) with conventional Nissen fundoplication CNF) has been prematurely closed,based on an interim analysis showing superiority of CNF over LNF, in terms of troublesome dysphagia, intrathoracic herniation or recurrent GORD. The cohort of patients operated received questionnaires to register reflux symptoms, general state of health and their feelings about operation with regular intervals up to 5 years.
82% returned their questionnaires. Reasons for no further cooperation were: 3 refusals (2 bad result, 1 fully asymptomatic, 10 address unkonwn, 1 died of brain tumour, 12 unknown).In the LNF-group, 50% were fully cured from reflux symptoms (CNF:54%), 48% were improved (CNF:34%) 2 % had unchanged symptoms (CNF:7%) , 5% were deteriorated only after CNF;general state of health after LNF: 70% felt improved, 19 % was unchanged and 13 % felt worse (CNF: 88, 7, 5 % resp).
After LNF and CNF 11 % and 5 % were on medical treatment ; over-all 18 patients graded their operation as “not worthwhile": 5 because they need PPI’s to control symptoms (the other 25 were happy with PPI’s as the outcome!), 13 for a variety of reasons (9 needing medication, 1 non-cardica chest pain, 1 ‘can’t vomit”, 1 dysphagia, 1 three reoperations).
There were no differences between LNF and CNF. For all four outcome measures, results after 5 years were about 5 % less than after two years. These data suggest that long-term results of antireflux surgery are acceptable/good taken into consideration that (i) 91% had refractory GORD as their initial indication for surgery, (ii) once succesfully operated patients opt for reoperation in 75%. If “being of antisecretory drugs” is the goal of surgery, LNF is long-term successful in 89% and CNF in 95%. If antireflux surgery is judged based on the results of one and the primary operation, the results are less satisfactory.

Vagus nerve injury after antireflux surgery

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Antireflux surgery is an attractive alternative for reflux patients refractory to medical therapy. Although antireflux surgery is effective in up to 90% of patients, side effects may occur such as vagus nerve injury. Little is known however on the incidence of vagus nerve injury and its relation to the outcome of surgery. In a large cohort of patients we prospectively evaluated vagus nerve function by the plasma pancreatic polypeptide (PP) response to insulin induced hypoglycemia.
Between 1988 and 2001, 137 patients who underwent primary reflux operation at the LUMC also underwent vagus nerve function tests before and 3-6 months after antireflux surgery. Vagus nerve dysfunction was defined as PP peak increment <47 pM (cut off in patients with truncal vagotomy). In addition, patients underwent 24 hour pH metry, esophageal manometry and gastric emptying tests (scintigraphy).
Of the 137 patients, 26 (19%) had evidence of vagus nerve injury based on abnormal postoperative PP responses. These 26 patients differed from the other 111 (no vagus injury) with respect to A) reflux control: total time pH<4 pre- to postoperative: 11.8 ± 1.8% to 8.4 ± 4.1% (ns) in vagus nerve injury vs. 10.6 ± 1.0% to 3.8 ± 1.2% ($p<0.001$) in patients with intact vagus nerve and B) gastric emptying: half emptying time for solids 100 ± 7 min to 101 ± 8 min (ns) in vagus nerve injury vs. 99 ± 3 min to 80 ± 3 min ($p<0.001$) in patients with intact vagus nerve. Pre and post LES pressure did not differ between patients with and without vagus nerve dysfunction. Postoperative symptoms of nausea, vomiting, dysphagia and diarrhoea were sign. ($p<0.05$) more prominent in the vagus nerve dysfunction group.
Conclusions: Accidental vagus nerve injury occurs in 19% of patients who underwent antireflux surgery, is associated with impaired reflux control and is not associated with a postoperative improvement in gastric emptying. Vagus nerve injury is associated with a negative outcome of antireflux surgery.

Influence of Hospital Volume on Mortality in Pancreaticoduodenectomy: a Meta-analysis

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Few elective surgical procedures are associated with higher operative risk than pancreaticoduodenectomy (PD). Numerous studies have shown that higher hospital volume is associated with lower postoperative mortality after PD. Nevertheless, few signs of centralization have been seen in Europe, because the higher volume-better outcome association for PD is still under debate. The aim of this study is to get the best evidence on centralization of PD by performing a meta-analysis of the available data.
A systematic search for studies comparing outcome after PD in high- and low-volume hospitals was employed. Studies were reviewed independently for design features, inclusion and exclusion criteria, cut-off values for high and low volume, and outcomes. The primary outcome measure was in-hospital mortality. Meta-analyses were performed for all included studies using different cut-off values for high- and low-volume.
Fifteen observational studies with a total number of 47,113 patients met the inclusion criteria and were included in a meta-analysis. Four hospital volume categories (I-IV) regarding PD were defined with cut-off values at 2, 5, 10, and 20 resections per year, respectively. A fixed-effects approach was used for studies that were not heterogeneous. The mortality rate in patients undergoing PD was significantly lower in high-volume hospitals than in low-volume hospitals, independent of the arbitrary cut-off values
Conclusion: The combined results of observational studies show an inverse relation between hospital volume and mortality in PD. Despite methodological shortcomings and case-mix in many studies, the best available evidence is in favor of centralization in PD.

Thoracoscopic splanchnicectomy: Technique and results in 72 patients with chronic pancreatitis

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The management of pain in patients with chronic pancreatitis is a challenge to every medical doctor.
The aim of this prospective study was to evaluate early and long-term pain relief provided by bilateral thoracoscopic splanchnicectomy. The surgical technique and results of the study are presented.
From August 1995 to December 2003, 72 patients with chronic pancreatitis underwent bilateral thoracoscopic splanchnicectomy because of pain. Data were collected prospectively. Pain intensity was registered before and after the operation by means of the Visual Analogue Scale (VAS). The use of analgesic drugs was registered before and after surgery. Median follow-up was 55 months (range 1-100).
The procedure was technically successful in 66 patients.
There were no major complications. All patients had immediate postoperative reduction of pain.
Sixty patients (80%) required opioids before operation and 20 patients (28%) at 12 months after operation. Median (range) VAS score dropped from 8 (7-10) to 3 (0-8)measured at 12 months after operation. Fifty-five percent of those patients with a long-term follow-up of 5 years or more were pain free or had significantly reduced pain.

Chronic mesenteric ischemia: from classical abdominal angina to single- and multivessel disease; experience in 102 patients

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Chronic mesenteric ischemia (CMI) is assumed to have a typical presentation (abdominal angina). CMI is often considered, but only rarely diagnosed. Data on incidence and clinical presentation are scarce. New diagnostic tools, such as gastric exercise tonometry and institution of multidisciplinary working groups may yield more insight in the prevalence and clinical spectrum of CMI. We therefore studied the epidemiology, treatment and outcome of CMI patients.
All patients referred nationwide from 1997-2003 to our multidisciplinary CMI working group were prospectively evaluated by interview, physical examination, angiography, duplex-ultrasound, and gastric exercise tonometry.
298 pts were referred for evaluation. Stenoses were found in 144 pts: 100 with single (94 CA, 6 SMA) and 44 multi vessel stenosis. CMI was diagnosed in 102 pts (72F/30M, mean age 48), 60 with single and 42 with multi vessel stenosis. Symptoms were weight-loss in 78%, post-prandial pain in 87%, and pain during exercise in 44% of pts. The 'classical triad' (postprandial pain, weight loss and abdominal bruit) was found in 24%. Single vessel pts: 43/60 were treated; improvement, after 1 year follow-up, in 33/43 pts (77%). Complication occurred in 1 pt (2%), a local jejunal infarction on presentation; 1-yr mortality was 0%. Multi vessel pts: 4 were not treated (1 died during work-up, 3 were unfit), 5 pts were urgently operated for mesenteric infarction (3 died). Of 33 electively treated pts, 5 pts died from multiple organ failure, all had extreme cachexia; 2 others died later of unrelated causes. The overall 1-yr mortality was 26%. Improvement of symptoms was 85% after 1 year.
Conclusions: CMI is not rare. Typical complaints are weight loss, pain after eating and during exercise. Both single and multi vessel stenoses can be treated successfully, but complications and mortality were almost exclusively seen in multi vessel patients. This distinction is therefore crucial in clinical management.

Laparoscopic-assisted versus open ileocolic resection for Crohn's disease: a randomized trial.

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Surgery for Crohn's disease is often a challenge. Inflammatory masses, fistula or abscesses can complicate the procedure. Performing the procedure laparoscopically is even a greater challenge. The aim of the study was to evaluate laparoscopic-assisted and open ileocolic resection for Crohn's disease in a randomized controlled trial.
Thirty patients were included in each arm. Primary outcome parameter was postoperative recovery in the 3 months after surgery, measured by quality of life questionnaires (SF-36, and GIQLI). Secondary parameters were surgical parameters, viz. operating time, morbidity, hospital stay, and costs.
Patient characteristics were not different. There was one conversion to an open procedure because of a large inflammatory mass, and twice to a hand-assisted laparoscopic procedure for more extensive resection due to present fistulas. Median operation time was longer in laparoscopic compared to open surgery (115 vs. 90 minutes; $p<0.003$). Hospital stay was shorter in the laparoscopic group (5 vs. 7 days; $p=0.008$). Morbidity within the first 30 days was different between the laparoscopic and open group (6% vs. 33%; $p=0.01$). Within 3 months there were two other readmissions in the laparoscopic group.
There was a significant change in quality of life on all scales of the SF-36 ($p<0.001$) and the GIQLI-score ($p<0.001$) in the 3 months after surgery. Quality of life declined in the first week, returned to baseline levels after 2 weeks and was improved 4 weeks and 3 months after surgery. However, this change in quality of life was not affected the type of surgery.
Overall costs were not different € 2461 for laparoscopic and € 2588 for open surgery ($p=0.89$)
Conclusions: Although patients were discharged earlier after laparoscopic surgery, recovery measured using quality of life questionnaires is not different for laparoscopic-assisted or open ileocolic resection. The laparoscopic approach is saver, while costs are comparable to the open approach.

Poor condition at operation is an independent risk factor in long-term survival of colo-rectal cancer patients

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Poor condition of patients at operation as determined by the Possum physiological score (PPS) is related to postoperative mortality and morbidity of colo-rectal cancer (CRC) surgery. To what extent long-term survival is affected by poor pre-operative patient status is not clear and is the subject of this study.
From 1990 to 2001 a consecutive serie of 674 patients survived resection for CRC and were included in this study. PPS, exclusive of age, at the time of surgery was calculated for all patients. Age was included as a seperate variable. Mean PPS used as cut-off point to determine low and high PPS patients. Mode of surgery, type of surgeon, TNM stage, tumor characteristics, use of adjuvant therapy, and data on long-term follow up were determined for all patients. Differences in survival were studied by Kaplan Meyer plots and independent risk factors for overall survival were studied by Cox multi-regression analysis. A risk profile considering the independent risk factors was made to predict reduction in survival.
Five year overall survival rate was 47.8% (low PPS patients 55.9%, high PPS patients 41.3%, P<.0001). Differences in overall survival were also found when patients in Stage I (60 vs 79.8 %, p=.01), Stage II (48.2 vs. 71.2 %, p=.0002), Stage III (34.7 vs 48.2 %, p=.04) and Stage IV(0 vs 2.1 %, p=.04) were analysed separately. Independent risk factors for long-term overall survival were TNM stage, radicality of resection, tumor differentiation, and PPS group. Age, sex, mode of surgery, surgeon (high volume vs. low volume), and tumor localization were not related to long-term survival. When more than one riskfactor was present a reduction in survival was found in Stage I (23.9%), Stage II (36,3%), Stage III (43,3%) and Stage IV (50, 3%).
Poor condition, i.e. higher physiological POSSUM scores, at operation is an independent risk factor for long-term survival in CRC patients.

TEM versus TME in early rectal cancer: a prospective comparative study

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In rectal cancer Total Mesorectal Excision (TME) is the gold standard if curation is intended. However, morbidity and mortality can be significant. Local excision of properly selected rectal cancers can provide long-term survival, with minimal morbidity, negligible mortality and excellent functional results. However, oncological outcome is under debate. Transanal Endoscopic Microsurgery (TEM) is a minimal invasive technique for the local excision of rectal tumors with excellent results in adenomas.
We compared prospectively the results after TME and TEM for T1 carcinomas. Parameters studied were operation time, blood loss, morbidity, mortality and hospital stay regarding safety. Also studied were recurrence rates, results of salvage surgery and survival regarding oncological outcome.
124 patients with 124 tumours were included. 50 patients underwent TEM and 74 patients underwent TME. Patient and tumor characteristics did not differ.
Operation time, blood loss, stoma formation rate and mild and severe complication rate were all significant lower in the TEM-group. There was no mortality after TEM, while mortality rate after TME was 4,1%.
Median follow-up after TEM was 21 months and after TME 24 months.
After TEM 8 patients developed a local recurrence (16%). All these patients underwent salvage surgery. No local recurrences or deaths were observed after salvage surgery. In 3 patients distant recurrences were observed (6%). Survival was 100%. After TME no local recurrences were observed and 3 patients developed distant metastasis (4,1%), of which 1 has died (survival 98,6%).
Conclusion: In T1 carcinomas, TEM is safe compared to TME without differences in distant recurrence rate and survival. Local recurrence rate is higher after TEM, but salvage surgery is possible and many patients are saved the adverse effects of TME.

The impact of (treatment for) rectal cancer on quality of life and societal functioning (Final report Maag Lever Darm Stichting project SWO 02-15)

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Short-term preoperative radiotherapy (pRT) and total mesorectal excision (TME) have each been shown to improve local control of disease in patients with resectable rectal cancer. Our RCT showed that pRT (5x5 Gy) reduces local recurrence rates at two years from 8.2 percent in the TME-only group to 2.4 percent in the pRT-group (Kapiteijn, NEJM 2001). Here we present results on quality of life and on paid and unpaid labor for the Dutch patients.
Health-related quality of life (HRQL) and paid labor were assessed using the Rotterdam Symptom Check List (RSCL). In the format of the RSCL, 3 items were added regarding voiding (alpha 0.76) and 7 regarding defecation (alpha 0.87). Further were added a 4-item scale on general satisfaction with sexual functioning (alpha 0.92), a 3-item scale on erectile dysfunction (0.98), a 2-item scale on ejaculatory problems (0.87), a 2-item scale on pain during intercourse (females, alpha 0.86), and 2 items on paid labor. For unpaid labour, the Health and Labour Questionnaire (HLQ) was used. Questionnaires were filled out at baseline, and at 3, 6, 12, 18 and 24 months after surgery. For the HRQL data pattern mixture models were fitted to assess the impact of pRT (data not missing at random).
Of the 1530 patients randomized, 1302 turned out to be eligible (85 percent) for the HRQL study. Over the 24 months, few differences in HRQL were seen between the two arms. Only at 3 months after surgery some differences HRQL were seen in favor of the TME-only arm. These patients reported fewer problems with defecation and with usual activities. At 12 months after surgery, patients in the TME-alone group had more often resumed paid labour. Significant decreased sexual activity and worse sexual functioning were seen in the pRT group at all times, both overall and on the sex-specific scales.
It seems that the benefit of pRT comes at the cost of sexual functioning, but not of overall quality of life.

Experienced problems in daily life by HPN-dependent patients (Final report Maag Lever Darm Stichting project SWO 01-16)

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Home Parenteral Nutrition (HPN) is a life-saving therapy in case of very serious intestinal problems. However, HPN changes life radically. The aim of the study was to get a better understanding of experienced problems in long-term HPN dependent patients. A survey was performed (n=48) among the patients of the ambulatory care clinics of two academic hospitals (response 76%). We used two techniques: questionnaires and structured open-ended interviews. The questionnaire included quality of life (Cantril's Ladder), health related functional status (Sickness Impact Profile/SIP68), way of coping (Utrechtse Coping Lijst/UCL), locus of control (Health Locus of Control), bowel disturbances, fatigue (Checklist Individual Strength/CIS), quality of sleep (Subjective Sleep Quality Scale/SSQS), anxiety (State-Trait Anxiety Inventory/STAI), depression (Depression Beck Inventory/DBI), social impairment (subscale Social Behaviour/SIP68), sexual functioning, and the strain of caregivers (Caregivers Strain Index/CSI). The interviews focused on somatic, psychological or social problems due to HPN dependency. The results showed raised levels of health related problems on all subscales, mean quality of life was 6.2. All respondents suffered from many somatic symptoms, 63% were severely fatigued, anxiety levels were not raised, 60% had (severe) depressive disorders, one third experienced sexual disorders and half of the respondents encountered various social impairments. In the interviews, most frequently reported problems were: anxiety with regard to medical complications, lack of freedom, 'other negative changes in moods & feelings', limitations in social life and being dependent. We conclude that patients who are HPN dependent experience many somatic symptoms. However, in the interviews they report psychosocial problems as a large burden in daily life. Therefore, alimentation teams should asses somatic as well as psychosocial aspects and address problems which may be present.

Irritable Bowel Syndrome: towards an integrated psycho-neuro-physiological approach (Final report Maag Lever Darm Stichting project WS 99-17)

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The pathophysiology of Irritable Bowel Syndrome (IBS) is poorly understood, but brain-gut axis alterations may play an important role in symptom generation. Furthermore, pharmacotherapy is frequently ineffective in treating the IBS complex, but recent studies suggest that psychotherapy may be helpful. This trial was designed to 1) further establish brain-gut interactions and 2) assess the efficacy of relaxation training (RT), a brief and inexpensive group intervention, in a large cohort of IBS patients. We assessed symptoms (diary), psychological parameters (questionnaires), rectal motor and sensory function (barostat) and autonomic nerve function (baroreflex sensitivity) at baseline in 105 IBS-patients (Rome II) and compared these to 40 healthy volunteers (HV). Subsequently, patients were randomized to RT or care as usual (controls). Follow-up occurred at 3, 6 and 12 months after treatment. At baseline, patients had impaired quality of life and more dysfunctional cognitions and inadequate pain coping compared to HV. The prevalence of anxiety and depressive symptoms was similar. Rectal compliance and pain thresholds were significantly decreased in patients compared to HV. Hypersensitivity to balloon distension was present in 47% of the patients and correlated with symptom severity and depressive symptoms. Autonomic function tests showed that neurocardiological adaptability in response to visceral stimuli (rectal pressure distensions) was impaired in patients compared to HV. Finally, IBS symptoms were significantly more improved in patients who received RT compared to controls at 3, 6 and 12 months after RT. Quality of life and medical consumption were not substantially affected by treatment. One year after therapy, 33% of patients in the RT group were improved versus 13% of controls.
Conclusion: The pathophysiology of Irritable Bowel Syndrome (IBS) is poorly understood, but brain-gut axis alterations may play an important role in symptom generation. Furthermore, pharmacotherapy is frequently ineffective in treating the IBS complex, but recent studies suggest that psychotherapy may be helpful.

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Conclusion: Several aspects of the brain-gut axis are different in IBS-patients compared to healthy volunteers. Relaxation training is an in-expensive and brief intervention, which improves symptom severity in IBS-patients.

Discrepancy between prescribed and administered energy in patients totally dependent on tube feeding.

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Hospitalised patients are often malnourished (25-62 %). The objective of this pilot study was to assess the difference between the energy intake and the prescribed energy in tube feeding in kcal/day and the factors causing this discrepancy.
Hospital medical records supplied data registered the previous day from 55 (adult) patients (24-84 years) totally dependent on tube feeding. Adequate administration of tube feeding was defined as 100% ± 10% of the prescribed amount. Data were analysed by SPSS 10.0.
Tube feeding was administered by: pump (n=37), portions (n=14) or drip (n=3) and by a combination of pump and portions (n=1). The difference between the intake and the prescribed enteral tube feeding was significant according to the Wilcoxon matched pairs signed rank test ($Z = - 5.3$; $p < 0.01$). The ratio energy intake versus prescribed energy was 86.6% (SD = 21%): pump 84.5% (SD = 23.6%), portions 93,5% (SD = 11.7%), drip 88.3% (SD = 18.1%). A deficit of 258 kcal/day (range –1900 to 190 kcal) was found. Thirty three patients (60%) were fed adequately and 22 (40%) inadequately. Graded to category: by pump: 21 patients (56.8%), by portions 10 patients (71.4%).
Adequate administration of tube feeding was only achieved in intensive care patients.
In general interruptions of various nature during feeding are the main causes for inadequacy.
Conclusions: Forty percent of the patients totally dependent on enteral tube feeding are inadequately fed according to the 24 hours registration in medical records. This may be one of the reasons for progressive mal-nutrition in hospital patients who are already malnourished. The current study seems to indicate that patients fed by portions are the most adequately fed.

Psychosocial problems in long-term HPN dependent patients

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Home Parenteral Nutrition (HPN) is a life-sustaining therapy for patients with irreversible gastrointestinal failure. Parenteral nutrition is given intravenously, 2 to 7 times per week for about 10-14 hours per day. Often, the patient is dependent on HPN for the rest of his or her life. Hyperalimentation teams focus on physical and technical aspects. The aim of the study is to describe thoroughly problems that HPN patients may experience in daily life. As part of a comprehensive study on problems due to HPN, patients were interviewed at home. The interviews were open-ended, but structured. The questions were: 1) which problem do you encounter due to HPN dependency (at a maximum of three problems, a problem may be of somatic, psychological or social origin)?; 2) which factors influence this problem?; and 3) which signs and symptoms do you experience? Data were analyzed through content analysis and a more in-depth qualitative analysis. The response was 76% (n=48). Psychosocial problems were mentioned most frequently as disturbing daily life. Almost one third of the group mentioned anxiety as a problem. They are afraid of medical complications and the future. Lack of freedom was reported by 29% of the respondents. Other negative moods than anxiety were frequently reported as well (27%), e.g. feeling alone, feeling aggressive, being emotional, not feeling healthy, not feeling understood, and feeling useless. Furthermore, respondents mentioned limitations in social life (21%), and being dependent (19%). The main somatic symptom was fatigue (17%). We conclude that HPN dependent patients experience many psychosocial problems. Besides the care for physical and technical aspects, the hyperalimentation team should also address psychosocial problems when caring for HPN dependent patients.

Randomised controlled trial of glutamine-enriched enteral feeding in very low birth weight infants: effect on clinical outcome

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Glutamine may improve feeding tolerance and growth in very low birth weight (VLBW) infants by providing oxidative substrate for enterocytes and increasing protein anabolism. We performed a randomised clinical trial (double blind) in 102 VLBW infants (GA < 32 weeks or BW < 1500 grams) to assess the effect of glutamine-enriched enteral feeding on short-term outcome. Infants were allocated to receive enteral glutamine supplementation (to a maximum of 0.3 gram/kg/day) or isonitrogenous isocaloric placebo supplementation (alanine) between days 3 and 30 of life. Supplementation was added to breast-feeding or preterm formula (2.4 gram protein/100 ml; casein-whey protein ratio 40:60). Analysis was performed on intention-to-treat basis. Patients in the glutamine (n=52) and control groups (n=50) had similar mean BW (SD) (1175 (378) and 1156 (318) grams), and GA (29.3 (1.7) and 28.7 (1.9) weeks). A BW < p10 occured in 17/52 (33%) infants in the glutamine group and in 12/50 (8%) infants in the control group. 31/52 (60%) infants in the glutamine group and 31/50 (62%) infants in the control group received complete (expressed) breast-feeding during the study period. Between glutamine and control groups no differences were found regarding age at finishing parenteral nutrition (13.6 (11.5-15.8) vs 14.9 (13.3-16.4 days), days without enteral feeding during study period 1.3 (0.6-2.0) vs. 1.7 (0.8-2.6) days), incidence of Bell's stage III necrotizing enterocolitis (2/ 52 vs. 2/50), age at regaining birth weight (9.7 (8.2-11.3) vs. 11.2 (9.7-12.7), weight on day 30 (1604 (1470-1737) vs. 1528 (1406-1649) grams), days on ventilator support during study period (7.6 (4.5-10.7) vs. 9.1 (6.3-11.9) days), age at discharge from the NICU (30.0 (21.9-40.1) vs. 33.9 (26.0-41.7) days) and death (7/52 vs. 4/50). This randomised controlled trial did not show improved short-term outcome in VLBW infants receiving glutamine-enriched enteral feeding.

Amino acid administration directly from birth onwards in very low birth weight (VLBW) infants is safe and results in anabolism.

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In utero, the fetus continuously receives amino acids (AA), which not only are used for protein synthesis, but also serve as an important fuel source. In the first few days of life, AA administration is often delayed because of assumed safety reasons, resulting in a catabolic state. Therefore, we determined safety and efficacy of administration of amino acids directly postpartum to VLBW infants.
The intervention group (AA, n=31) intravenously received 2.4 g AA/(kg.d) directly from birth onwards; the control group (C, n=40) received as from postnatal day two 1.2 g AA/(kg.d) and as from postnatal day three 2.4 g/(kg.d).
Nutritional intake, use of medication, blood gas, and blood glucose concentration were recorded daily. Blood urea nitrogen (BUN) concentrations and nitrogen balances were measured on day two and day four.
Clinical differences between both groups were not significantly different (birth weight (g ± SD): AA 1069 ± 260 vs C 987 ± 264; gestational age (wk ± SD): AA 28.9 ± 2.2 vs C 28.5 ± 2.2). In addition, neither blood gas analysis, nor the use of medication, nor the non-protein energy intake showed any significant differences between both groups.
Glucose levels were significantly lower in the AA group on day two (in mmol/l (min-max); AA 3.9 (1.5 – 12.5) vs C 5.8 (1.3 – 11.4); p = 0.002). On all other days, glucose concentrations were not significantly different between the AA and C group. BUN concentrations were significantly higher in the AA group on day 2 and 4 (in mmol/l (min-max); day 2: AA 9.5 (3.1 – 14.1) vs C 5.9 (2.3 – 11.3); p=<0.001; day 4: AA 8.9 (2.5 – 15.6) vs C 5.2 (1.8 – 22.3); p=<0.001).
On day 2, nitrogen balance was significantly higher in the AA group (in mg N/(kg.d) ± SD; AA 152 ± 101 vs C -81 ± 74; p=<0.001). On day 4, nitrogen balance did not differ between both groups.
Conclusions: A high dose of amino acids can be administered safely to VLBW infants from birth onwards and results in an anabolic state in these infants.

High intestinal utilization of threonine in piglets

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Threonine is an important essential amino acid that is utilized in high amounts by the intestine. Intestinal threonine can be oxidized, incurporated into constitutional proteins or can be used for (glyco)protein synthesis that are secreted (e.g. mucins). We hypothesized that threonine is mainly used for secretory (glyco)protein synthesis and not for constitutive protein synthesis or oxidation.
To quantify the intestinal metabolic fate of dietary and systemic threonine in piglets during low protein (LP) and high protein (HP) isocaloric diet.
Intraduodenal and intravenous infusions of [U-^{13}C]threonine were used to determine the utilization of threonine in the small intestine of 16 piglets. Portal and arterial blood samples were collected to determine first-pass mucosal uptake, arterial portal-drained viscera uptake and oxidation of threonine using GC-MS and IR-MS techniques. Protein content and isotopic enrichment of threonine (GC-(IR-)MS) was measured in four segments of the intestine.
The equivalent of 88% of the dietary protein intake was utilized in the portal-drained viscera during HP feeding and 98% during LP feeding. 59% of the intestinal threonine uptake was incorporated in constitutive proteins during HP diet and 74% during protein restriction. Threonine oxidation accounted for 3% and 4% of the intestinal uptake during HP and LP feeding respectively.
Conclusions: The intestine is the major site of the whole body threonine utilization. The high rate of intestinal threonine utilization is mainly caused by incorporation of threonine in constitutive proteins.

Presence of non-cachectic tumour prohibited the post-operative rise in arginine and NO production in vivo in mice.

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We previously observed that patients with cancer have low pre-operative plasma arginine (Arg) levels. When undergoing surgery, this Arg deficiency may compromise recovery because Arg and its product nitric oxide (NO) stimulate wound healing and the immune response. We therefore investigated to what extend the presence of tumour affected the response of Arg and NO production to surgical trauma.
Laparotomy (LAP) was used as a model for surgical trauma in a non-cachectic mouse tumour model. The following groups were studied, either with or without LAP: controls (C), mice with small tumours (ST, <15% of body weight) and mice with large tumours (LT, >15% of body weight), resulting in six experimental groups (n=10-15 per group). One day after LAP, a primed-constant intravenous infusion of L-[*guanidino*-$^{15}N_2$-$^{2}H_2$]arginine and L-[*ureido*-^{15}N]citrulline was given to measure Arg and NO production. Blood was sampled from the carotid artery. Tracer-tracee ratio's were determined using LC-MS and plasma amino acid concentrations using HPLC. Significance was tested using Mann-Whitney.
Compared with C, baseline Arg and NO production (nmol/10g/min) were higher in ST and LT (Arg: 42±3 (C) vs. 54±7 (ST) vs. 79±7 (LT), $p<0.05$; NO: 1.1±0.1 (C) vs. 1.3±0.3 (ST) vs. 1.7±0.2 (LT), $p<0.05$). In C, LAP increased Arg and NO production (Arg: +29±2%, $p<0.05$; NO: +27±3%, $p<0.05$). In ST, Arg and NO production did not increase after LAP. In LT, LAP even decreased Arg and NO production (Arg: -24±2%, $p<0.05$; NO: -35±4%, $p<0.05$).
Conclusion: In healthy controls, surgery increased Arg and NO production. In tumour-bearing mice, this post-operative response was prohibited, probably because of the elevated baseline Arg and NO production in tumour-bearing mice. This might affect post-operative recovery negatively. The ability of pre-operative Arg supplementation to restore this non – response deserves investigation.

In vivo glutathione synthesis measurements in human liver and muscle; comparison between weight losing and non-weight losing cancer patients

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Cancer cachexia is a syndrome characterized by severe weight loss and protein depletion. We hypothesized that diminished substrate availability under these conditions impairs synthesis of glutathione (GSH), the most abundant intracellular antioxidant. GSH depletion may be of special clinical relevance, in view of the inflammatory status and subsequent oxidative stress that is frequently encountered in patients with advanced cancer.
Thus, we compared weight-losing pancreatic cancer patients (n=6) with weight-stable patients with colorectal liver metastases (n=5) undergoing surgery aiming either for a Whipple's procedure or hepatectomy. An iv infusion with 2H2-glycine was started before surgery and continued for 6 h. At t=2 h and before closure of the abdomen, biopsies were taken from liver and rectus abdominis muscle. Fractional synthesis rate (FSR) of GSH was calculated from the rate of increase in isotopic enrichment in GSH using standard equations.
At t=2 h, mean (SEM) enrichment in GSH was 1.6 (0.5)% in liver and 0.58 (0.07)% in muscle. No further increase was found in the liver while enrichment in muscle rose linearly to 1.18 (0.2)% during the following 2 h. FSR (%/day) was 887 (142) and 208 (66) for liver and muscle respectively (p=0.028). GSH concentration (µmol/g ww) was 1.9 (0.2) in liver and 0.8 (0.1) in muscle (p=0.005). Absolute synthesis rate (µmol/g/day) was 14.7 (3.8) and 3.5 (1.5) for liver and muscle respectively (p=0.018). No significant differences were observed between weight-losing and -stable patients.
Conclusion: In vivo GSH synthesis rate in human solid tissues can be measured using stable isotopes. Both fractional and absolute GSH synthesis, as well as GSH concentration is higher in liver than in muscle but not different between weight-losing and -stable cancer patients. The enrichment plateau that was reached within 2 h in liver indicates that hepatic GSH synthesis rates found in this pilot-study may be an underestimate of the actual value.

Vagal Stimulation Attenuates Muscularic Inflammation and Post-operative Ileus Induced by Intestinal Manipulation

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Post-operative ileus (POI) following surgery results from the activation of resident macrophages in the intestinal muscularis, leading to local inflammation. Recently, macrophage activation was shown to be attenuated by cholinergic (vagal) efferent activity. Here, we evaluated whether electrical stimulation of the vagal nerve effectuates a reduction in muscular inflammation resulting from intestinal manipulation.
Mice underwent either laparotomy (L) or intestinal manipulation (IM), and were subjected to either sham surgery or electrical stimulation of the left vagal nerve for 5 min pre- and 15 min post-operatively (1 or 5 V pulse where indicated, 2 ms, 5 Hz). After 24 hrs, gastric emptying of a semi-liquid meal was determined by scintigraphic imaging. Granulocyte infiltration was determined by measurement of myeloperoxidase (MPO) activity.
Vagal stimulation did not affect gastric emptying after L. However, gastric emptying was significantly delayed after IM compared to L (retention at 60 min. after gavage: 14+/-4% (L) and 57+/-9% (IM), n=3-4, $p<0.05$). IM combined with electrical stimulation of the vagus nerve (IM+5V) prevented the IM-induced delay in gastric emptying (retention at 60 min. 27+/-7%). Concurrently, IM induced an inflammatory response reflected by an increase in MPO activity in the ileal muscularis compared to L (30.7+/-14.7 (IM) and 6.4+/-2.3 (L) U/g, n=4-8, $P<0.05$). This MPO increase was counteracted by peri-operative stimulation of the vagal nerve in a voltage-dependent fashion (IM+1V: 16.3+/-5.9; IM+5V: 7.7+/-1.2 U/g). Thus, the recruitment of inflammatory infiltrates into the intestinal muscularis and the subsequent development of POI following intestinal manipulation can be attenuated by peri-operative vagal nerve stimulation. These results suggest a potent neuro-immuno modulation of the network of resident macrophages in the GI tract that involves the vagal nerve.

Low dose ileal oil perfusion increases satiety in humans

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Lipids delivered to the ileum activate the so-called 'ileal brake' which delays gastric emptying and intestinal transit. Little is known about the effect of the ileal brake on satiety. We studied the effect of ileal oil (low dose emulsions) on satiety after a liquid meal replacement. Plasma PYY and CCK levels (markers for ileal and duodenal brake, respectively) were measured. Sixteen healthy, lean volunteers (9 F; mean age 25.8±2.6 yr) were intubated with a naso-ileal tube and participated randomly in 3 experimental days. On one day subjects drank at t=0 min the meal containing 3 g fat (0.92 MJ; formula A) and the ileum was perfused with placebo for 45 min beginning at time t=105 min. The other days volunteers drank a fat-free version of the meal (0.82 MJ) and the ileum was perfused with an emulsion containing 3 (formula B) or 10 g (formula C) long-chain triglyceride oil. Satiety parameters were scored (using line scales) and blood samples were drawn at regular intervals until 240 min postprandially. Both meal types (with and without fat) induced satiety. During and after the ileal perfusion, satiety parameters were significantly increased both in B and C vs A ($p<0.05$). The integrated PYY response during ileal perfusion in C (incremental AUC: 148±42 pM*min, $p<0.05$) but not after B (63±42 pM*min) was significantly increased over A (14±42 pM*min). Surprisingly, the CCK response during ileal perfusion was significantly ($p<0.05$) higher in B (17±3 pM*min) and C (31±3 pM*min) compared to A (-4±3 pM*min). CCK response to ileal perfusion in C was higher than in B ($p<0.05$). 3 and 10 g oil delivered to the ileum increase and prolong postprandial satiety to the same extent after ingestion of a liquid meal replacement, when compared to 3 g of oral oil ingestion. Plasma PYY does not represent the ileal brake effect of low dose intraileal oil on satiety. Despite distal ileal delivery, significant amounts of CCK were released in response to the 3 and 10 g oil emulsions.

Effect of intravenous PYY infusion on pancreatico-biliary secretion

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The negative feedback on pancreatico-biliary secretion induced by ileal nutrients has been well documented. Plasma PYY secretion represents activation of the 'ileal brake'. However, the effect of PYY on pancreatico-biliary secretion in humans is unknown. The effect of i.v. PYY infusion on basal, sham feeding (MSF) and feeding stimulated pancreatico-biliary secretion was studied in eight healthy volunteers (5F; mean age 26±3 yr). They participated in a placebo-controlled, double-blind, randomized study consisting of two experiments on separate days. Subjects were intubated with a 4-lumen naso-jejunal tube. Duodenal juice samples were aspirated while a recovery marker perfused the duodenum. After a basal hour, secretion was stimulated by MSF followed by a 2 hr continuous jejunal delivery of a mixed liquid meal (100 kcal/hr). Concentrations of enzymes, bilirubin and PEG were analyzed and outputs were calculated. PYY was infused at a dose of 30 pmol*kg-1*min-1 during 3.5 hr (raising plasma PYY levels from 24±1 to 65±2 pM; $p<.01$). Basal outputs of amylase, lipase, trypsin and bilirubin were not affected by PYY infusion. During MSF in the placebo experiment, lipase output increased from 25±5 to 52±9 kU/30 min ($p<.01$), trypsin output increased from 57±12 to 87±13 U/30 min ($p<.05$), and the bilirubin output increased from 7±2 to 13±2 mmol/30 min ($p<.01$). During PYY infusion no significant increase in pancreatico-biliary secretion by MSF was observed. Jejunal feeding however, significantly ($p<.01$) increased the outputs of all parameters equally in both the placebo and PYY infusions (lipase 74±12 vs. 82±11 kU/30 min; trypsin 102±18 vs. 99±15 U/30 min; bilirubin 23±5 vs. 21±4 mmol/30 min resp.).
Conclusions: Infusion of PYY to physiological postprandial levels does not influence basal outputs of amylase, trypsin, lipase or bilirubin. PYY only impaired pancreatico-biliary secretion during the cephalic phase but not during the intestinal phase of nutrient digestion.

Modulation of gene expression by vegetables in normal colorectal mucosa of sporadic colon adenoma patients and healthy controls

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Globally, cancer of the colon and rectum is the fourth most common incident cancer and cause of death from cancer. The evidence from epidemiological and experimental studies that vegetables reduce the risk of colorectal cancer is convincing. However, the involved genes and genetic pathways are not clear. Microarray technology makes it possible to assess the effect of a specific vegetable diet on the expression of multiple genes. Therefore, a human dietary intervention study was carried out to identify the genes the expression of which is modified in vivo in normal human colorectal mucosa by vegetables. Twenty female adenoma patients and eight healthy controls were randomly split into two groups of ten and four persons respectively, receiving either a decreased (= 75 g/day) or increased (= 300 g/day) amount of vegetables for a period of two weeks. In order to assess effects on gene expression at target level, before and after the intervention colorectal biopsies from healthy mucosa tissue were collected. Total RNA was isolated from the biopsies to measure gene expression of 597 toxicologically relevant genes by means of microarrays. Comparison of pre- and post-intervention samples shows that 20 genes were modulated which are related to (colon)carcinogenesis, including c-fos proto-oncogene, ornithine decarboxylase and cyclo-oxygenase-2. In contrast to a decreased intake of vegetables, an increased intake results in suppression of genes involved in cell proliferation and activation of pro-carcinogens. Some of these genes play a role in known colon carcinogenic pathways and could thus be new targets for chemoprevention.

Apolipoprotein C3-deficiency results in Diet-induced Obesity and Insulin Resistance in Mice

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Apolipoprotein C3 (apoC3) is a strong inhibitor of lipoprotein lipases (LPL), a key enzyme in fatty acid delivery to muscle and adipose tissue. Our aim was to study whether the absence of apoC3 accelerates the development of obesity and insulin resistance. Apoc3-/- mice and wild type littermates were fed a high fat (46 energy %) diet for 20 weeks. Body weight and food intake were assessed weekly. Adipose tissue fatty acid uptake and body fat composition were analyzed at the end of the study. Insulin sensitivity was determined using hyperinsulinemic euglycemic clamps with 3H-glucose as a tracer. After 20 weeks of high fat feeding apoc3-/- mice were more obese than wild type littermates (42.8 ± 3.2 vs. 35.2 ± 3.3 g, $p<0.05$). This increase in body weight was entirely explained by increased body lipid mass (16.2 ± 5.9 vs. 10.0 ± 1.8 g, $p<0.05$). No significant difference in adipocyte size was observed as compared to wild type littermates. In adipose tissue fatty acid uptake from plasma triglycerides (TG) was significantly higher in apoc3-/- mice, indicating enhanced LPL-mediated fatty acid delivery to this tissue. The uptake in adipose tissue of albumin-bound fatty acids, used as a measure to determine LPL-independent uptake of fatty acids, did not differ from that of control mice. As expected whole body and hepatic insulin sensitivity were decreased in apoc3-/- mice compared to wild type littermates (46 and 26%, respectively).
Absence of apoC3, the natural LPL inhibitor, enhances fatty acid uptake from plasma TG in adipose tissue, which in turn leads to higher susceptibility to diet-induced obesity and insulin resistance. Therefore, apoC3 is a potential target for treatment of obesity and insulin resistance.

Intracerebroventricular Neuropeptide Y infusion precludes inhibition of glucose and VLDL-production by insulin.

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Recent evidence demonstrates that hypothalamic insulin signaling is required for inhibition of endogenous glucose production (EGP). The downstream mechanisms responsible for the effects of hypothalamic insulin receptor activation on hepatic fuel flux remain to be established. To establish if downregulation of Neuropeptide Y (NPY) release by insulin is mandatory for its capacity to suppress glucose production, we examined the effects of a continuous intracerebroventricular (i.c.v.) infusion of NPY (10 µg/h for 3-5 hours) on glucose flux during a hyperinsulinemic euglycemic clamp in mice. We also evaluated the effects of i.c.v. NPY administration on free fatty acid- and glycerol flux and very low-density lipoprotein (VLDL) production in this experimental context. In basal conditions, none of the metabolic parameters was affected by NPY infusion. In hyperinsulinemic conditions, peripheral glucose disposal was not different between vehicle- and NPY-infused animals. In contrast, hyperinsulinemia suppressed endogenous glucose production by approximately 8% vs. 30 % in NPY- vs. vehicle-infused mice respectively ($P<0.05$). Also, VLDL-production was significantly higher during hyper-nsulinemia in NPY- compared with vehicle-infused mice (97.5 ± 18.0 vs. 54.7 ± 14.9 µmol/kg/h, $P<0.01$). These data suggest that the neuro-hysiological action of insulin to downregulate hypothalamic NPY release is a prerequisite for its ability to suppress hepatic fuel production, whereas it is not mandatory for its capacity to modulate glucose disposal or lipolysis.

Altered Tissue-Specific VLDL-derived Fatty Acid Partitioning may be Involved in the Ritonavir-Associated Lipodystrophy Syndrome

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The introduction of highly active antiretroviral therapy caused a significant decrease in the morbidity and mortality associated with HIV-infection. Currently available drugs, however, can cause the lipodystrophy syndrome, which is characterised by changes in body fat distribution and several metabolic abnormalities, such as hyperlipidaemia and insulin resistance. The aim of this study was to investigate the effects of ritonavir (RTV) on lipid and glucose metabolism. We studied the effects of RTV on triglyceride (TG) production and clearance and on basal and insulin-mediated glucose metabolism in female APOE*3 Leiden transgenic mice, which have a humanised lipoprotein profile. After administration of RTV for 3 weeks at 35 mg/kg bodyweight/day, plasma TG increased from 2.7 to 5.4 mmol/l (P=0.004) and plasma cholesterol from 12.7 to 15.3 mmol/l (P=0.017). When compared to untreated mice, hepatic VLDL-TG production was not increased. After an intra-gastric olive oil bolus, a significantly increased postprandial plasma TG response was observed at 4 hours after administration. In vivo lipolysis of labelled VLDL-like particles showed a significantly decreased uptake of fatty acids derived from plasma TG in subcutaneous fat, but not in visceral fat, in RTV-treated animals when compared to controls. In the livers of RTV-treated mice an increased triglyceride content was found compared to controls (245± 36 versus 93± 49µg TG/mg cell protein, P=0.014). Concomitantly, hyperinsulinaemic euglycaemic clamp analyses showed a significantly diminished insulin-mediated inhibition of hepatic glucose production in RTV -treated mice (10% inhibition versus 50% in controls), but not of insulin-mediated whole body glucose uptake.
We propose that alterations in tissue-specific partitioning of fatty acids, derived from plasma VLDL may be involved in the ritonavir-associated lipodystrophy syndrome.

24 Hours Fasting Differentially affects Hepatic and Muscle Insulin Sensitivity

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Short-term fasting readily induces hepatic steatosis. Evidence is accumulating indicating that hepatic accumulation of triglycerides is involved in hepatic insulin resistance. The purpose of the present study was to document the effects of short term fasting (24 hours) on insulin sensitivity in liver and skeletal muscle in relation to 1) tissue accumulation of TG and 2) changes in mRNA expression of metabolically relevant genes. Fasting in wildtype mice resulted in hepatic insulin resistance with decreased suppression of hepatic glucose production (43 ± 7% after fasting compared to 73 ± 14% in control group, $p<0.05$) in the presence of hepatic steatosis (71±19 versus 12±6 µg/mg protein, $p<0.05$). In muscle, however, 24h fasting resulted in increased insulin sensitivity with increased muscle glucose uptake (5.6±2.1 versus 1.2±0.2% per g tissue, $p<0.05$) without changes in muscle triglyceride content (25$\pm$7 versus 23±7 µg/mg protein, ns). In liver, 24h fasting resulted in increased mRNA expression of PGC1 and PEPCK, promoting gluconeogenesis, whereas expression of glycogen phosphorylase, promoting glycogenolysis, was decreased. 24h fasting decreased mRNA expression of SREBP1c, a transcription factor mediating insulin suppression of PEPCK. 24h fasting increased mRNA expression of genes promoting TG synthesis (PPARα, DGAT1 and DGAT2), but decreased mRNA expression of genes involved in fatty acid synthesis (SREBP1c, FAS and ACC1). In muscle, increased mRNA expression of genes promoting glucose uptake (PGC1 and GLUT-4) was found, as well as increased expression of genes promoting lipogenesis (PPARα, FAS, ACC1, DGAT1 and DGAT2) and PPARα, promoting β-oxidation, whereas SREBP1c mRNA was found to be decreased. In conclusion, 24h fasting induces hepatic insulin resistance in combination with steatosis, whereas muscle insulin sensitivity increases without changes in muscle TG content. Therefore, 24h fasting induces differential changes in tissue-specific insulin sensitivity.

Peginterferon alfa-2b alone or in combination with lamivudine for chronic HBeAg-positive Hepatitis B: a randomized controlled trial

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The efficacy of peginterferon α-2b (PEG-IFN) in chronic hepatitis B is unknown. It is also unknown whether combination therapy with PEG-IFN and lamivudine is superior to PEG-IFN monotherapy. In an international, multicenter study 266 HBeAg-positive chronic hepatitis B patients were randomly assigned to receive either 100 μg/week PEG-IFN and placebo (n=130) or combination therapy with 100 μg/week PEG-IFN and 100 mg/day lamivudine (n=136). Treatment duration was 52 weeks. From week 32 to week 52 PEG-IFN dose was reduced to 50 μg/week in both treatment arms. All patients were followed-up until week 72. Response was defined as serum HBeAg negativity at end of therapy and follow-up. All patients were HBV-DNA positive (hybridization assay) and had ALT values more than twice above normal at baseline.
At the end of therapy response was 29% for PEG-IFN monotherapy and 44% for PEG-IFN-lamividine combination therapy (p=0.01). In contrast, end of follow-up response was equal for both treatment groups: 36% for monotherapy and 35% for combination therapy (p=0.91). Similar response patterns were seen when response was assessed by serum HBV-DNA suppression and change in ALT levels. In multivariate analysis HBV genotype, prior IFN therapy, and serum baseline levels of HBV-DNA and ALT were independent predictors for sustained response. Response at end of follow up was 47% for genotype A, 44% for genotype B, 28% for genotype C and 25% for genotype D (p=0.03). Side effects were comparable in both treatment groups and similar to those of conventional IFN. PEG-IFN dose was reduced in 22% and discontinued early in 9% of the patients.
PEG-IFN is effective for HBeAg-positive chronic hepatitis B, and combination therapy with PEG-IFN and lamivudine is not superior to PEG-IFN monotherapy. HBV genotype is an important predictor of response to treatment, suggesting that future intervention studies for chronic hepatitis B may need stratification for genotype.

Abnormal hepatocystin caused by truncating *PRKCSH* mutations lead to autosomal dominant polycystic liver disease

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Mutations in *PRKCSH* encoding for the protein hepatocystin, cause autosomal dominant polycystic liver disease (PCLD; MIM 174050), which is clinically characterized by the presence of multiple liver cysts. PCLD has been documented in families from Europe (Netherlands, Belgium, Finland) as well as from the United States. Here, we report results from extensive mutational analysis of the *PRKCSH* gene in a group of 14 PCLD families and 65 singleton cases with multiple simple liver cysts from Dutch and Finnish descent. We identified *PRKCSH* mutations in 12 families as well as in 3 sporadic cases. In 8/10 Finnish families we detected the 1437+2delTG splice site mutation. In Dutch families we found 2 other mutations that affect correct splicing of *PRKCSH* (292+1 G>C 2 families, 1338-2 A>G, 1 family). In another Dutch family we detected a novel deletion (374-375delAG) in exon 6, predicting an abnormal shortened protein. Investigation of the carrier haplotypes identified a common founder chromosome in unrelated individuals in each of the 3 identified splice site mutations. In two Finnish families with dominantly inherited PCLD and in 62/65 sporadic cases with multiple simple liver cysts, we failed to demonstrate any *PRKCSH* mutation. This corroborates with the notion that autosomal dominant polycystic liver disease is genetically heterogeneous. On the basis of our results, we propose that genetic screening for *PRKCSH* gene mutations should be limited to patients with either a positive family history for PCLD or to those who have severe polycystic liver disease.

Viral dynamics during a 24-weeks course of tenofovir in patients with lamivudine-resistant hepatitis B virus mutants

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Tenofovir, licensed as a HIV drug, has also activity against lamivudine-resistant HBV mutants. To describe the efficacy of tenofovir more precisely in vivo, we have investigated the effect of tenofovir on hepatitis B virus (HBV) viral dynamics in lamivudine resistant patients.
Eleven chronic HBV patients on lamivudine for 72-382 weeks (median: 176 weeks) with breakthrough HBV DNA and the presence of an YMDD mutation received “add-on” tenofovir 300 mg once daily, while maintaining their existing therapy.
Sequential sera, taken at day 1; t=0 and t=8 hours, day 2, 4, 7, 10, 14, 21, 28 and thereafter every 4 weeks, were tested for HBV DNA using validated quantitative PCR. We applied individual non-linear fitting and mixed effect group fitting.
Mean baseline log HBV DNA was 8.31±1.07 (median 8.62; range 6.48-9.76 log HBV DNA). Application of tenofovir resulted in a mean log HBV DNA decline of 1.37±0.51 in the first phase, 2.54±0.91 after 4 weeks of tenofovir treatment and a mean decline of 4.95±0.90 log HBV DNA after 24 weeks of treatment. The median effectiveness of blocking viral replication in the individual fit was 93% (range 73%-99%) for η=0 and 93% (range 59%-99%) for η=1. The half-life of free virus is 21.18 hours (median; range 16.23-47.34) and the half-life of infected hepatocytes is 5.77 days (median; range 3.06-33.24) for the individual fit.
These data show that tenofovir has an average good efficacy in blocking viral replication in HBV patients with lamivudine induced mutant viruses, but large individual variability exists.

Viral dynamics during PEG-interferon alone and in combination with lamivudine.

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To evaluate if viral dynamics during therapy predicts response (HBeAg negativity 6 months posttreatment), we analyzed viral decline in 266 HBeAg positive chronic hepatitis B treated with pegylated interferon alpha-2b (PEG-IFN) monotherapy or its combination with lamivudine. Serum HBV-DNA levels were measured monthly during therapy and 6 months posttreatment. In 35 patients HBV DNA was measured frequently during the first month (days 0-4, 7, 14, 21, 28) to assess early HBV dynamics. Response was achieved in 35% of the combination therapy group and 36% of the monotherapy group. Throughout the study period, we found a significantly faster HBV-DNA decline in the combination therapy group, compared to the monotherapy group. Responders showed a greater HBV DNA decline in both groups: In the combination therapy group HBV DNA decline in the first two months of therapy was 3.9 log in responders and 3.5 log in non-responders (p=0.001). In the monotherapy group HBV DNA in the first two months was 1.1 log in responders, compared to 0.7 log in non-responders (0.006). After 12 weeks of therapy there was no HBV DNA decline in non-responders receiving monotherapy. Analysis of HBV DNA decline during the first month with frequent sampling showed a biphasic decline of HBV-DNA in the combination therapy group. The efficacy of combination therapy was 94.9%. In this group HBV-DNA decline during the first week was associated with response. In the monotherapy group a more complex HBV-DNA decay pattern was found, not fitting a biphasic model.
In conclusion combination therapy with PEG-IFN and lamivudine is more effective in suppressing HBV replication than PEG-IFN. This did not result in enhanced sustained response rates. Only for patients treated with combination therapy initial decline of HBV-DNA was indicative of response. For patients treated with PEG-IFN alone response was associated with HBV-DNA decline after 12 weeks, probably due to enhanced immune reactivity.

Improved results of resection of hilar cholangiocarcinoma (Klatskin tumors): A single-center, 15-year experience

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Radical resection of hilar cholangiocarcinoma (HC) is difficult due to its proximal infiltration into the biliary tree and its frequent involvement of the bifurcation of the portal vein. In the nineties, several studies showed improved results of more aggressive resection of HC in combination with extended liver resection. Based on these results, we changed our treatment strategy towards performing more resections combined with (extended) hemihepatectomy, with complete excision of segment 1. The aim of this study was to assess the outcome of this changed strategy in terms of morbidity and mortality, microscopical tumor clearance and patient survival.
A total of 99 patients underwent resection of HC from1988 to 2003. The patients were divided into 3 groups (mean age 60±1 years(±SEM)): group 1 (’88-’93, n=45), group 2 (’93-’98, n=25) and group 3 (’98-’03, n=29). Proximal infiltration of HC was classified according to the Bismuth-Corlette system (I-IV). Patients routinely received postoperative radiotherapy (55Gy).
Compared to group 1, there were significantly more patients with type III and IV tumors in groups 2 and 3 (38% vs. 64% and 72%, resp., $p<0.05$). The proportion of hilar resections in combination with (extended) hemihepatectomy increased from 9% in group 1 to 72% in group 3 ($p<0.01$). In group 3, 15 patients underwent excision of segment 1. The number of margin negative resections increased from 13% and 32% in group 1 and 2, resp., to 59% in group 3 ($p<0.05$). There were no significant differences in morbidity (66%) or mortality (15%). The mean survival time (months) increased from 31±6 in group 1, to 43±5 in group 3 ($p<0.01$). In group 2 and 3, 4 and 17 patients are alive at the completion of this study, resp.
Conclusion: Resection of HC in combination with (extended) hemihepatectomy and complete excision of segment 1, has resulted in more margin negative resections and an improved survival, without increasing postoperative morbidity and mortality.

Exacerbation of chronic hepatitis B in relation to genotype and response of treatment with pegylated interferon alone or its combination with lamivudine

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Flares of inflammatory activity are a well-known phenomenon during treatment with interferon and after withdrawal of lamivudine for chronic hepatitis B. Although flares are thought to represent immune-mediated clearance, little is known about their relation with response to antiviral treatment. We investigated the relation between flares, HBV genotype and response (serum HBeAg loss at end of follow-up) in a multicenter randomised controlled study. A total of 266 chronic HBeAg-positive hepatitis B patients were randomly assigned to receive 100µg PEG-IFN weekly combined with daily 100mg lamivudine or placebo for 52 weeks. The follow-up lasted 24 weeks. Sixty-eight patients (26%) exhibited a flare, defined as a 3-fold increase in alanine aminotransaminase (ALT) compared to baseline, with 35 (52%) flares in the combination-therapy and 33 (48%) in the mono-therapy. Of the total 68 flares, 30 (44%) were reported on treatment and 38 (56%) during follow-up. Responders (n =20) experienced more often an on-treatment flare than non-responders, 12 (60%) vs. 18 (38%), respectively (p = 0.09). On-treatment flares occurred predominantly in patients with genotype A, 12/75 (75%) compared to genotypes B, C and D, 18/52 (35%), p = 0.004. In comparison with other genotypes, post-treatment flares were more frequently reported in genotype D, respectively 18 (44%) vs. 20 (74%), p = 0.014. Of patients with flare best response rates were found in genotype A patients 8 (50%) compared with other genotypes 12 (23%) with p = 0.039. Mean elevation of ALT during exacerbation was significantly higher in responders (772 IU/L) than non-responders (532 IU/L; p = 0.028). Multivariate analysis showed the altitude of the ALT during the flare as the only independent predictor for response, p = 0.042. In conclusion, patients with a flare seem to react better to therapy if they have genotype A and on-treatment flare, although higher ALT levels during flare are the only independent predictors for response.

Liver histology in chronic hepatitis B patients after 1 year of treatment with pegylated interferon alpha-2b in combination with lamivudine or placebo.

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The two established therapies for chronic hepatitis B (CHB), interferon and lamivudine, have shown to improve liver histology. We studied the effect of pegylated interferon alpha-2b (PEG-IFN) therapy alone and in combination with lamivudine on liver histology. A total of 266 HBeAg-positive CHB patients were treated for 52 weeks with PEG-IFN 100 µg/week in combination with either lamivudine 100 mg/day or placebo in a double-blinded, randomized, multi-center study. PEG-IFN dose was halved after 32 weeks of treatment. Liver biopsies were requested before treatment and at the end of treatment (optional). All biopsies were blinded and scored according to the Ishak system which includes a necroinflammatory score (0-18) and a fibrosis score (0-6). Paired and evaluable biopsies were available for 110 patients. The mean baseline scores of the two treatment groups were comparable. Overall, inflammation score improved (mean score 5.5 pretreatment vs 3.9 posttreatment, $p<0.001$) and there was a slight progression in fibrosis (mean score 2.4 pretreatment vs 2.7 posttreatment, $p=0.03$). Necroinflammatory score improved in 25 patients (48%) in the combination group and in 31 patients (53%) in the PEG-IFN monotherapy group. Fibrosis score improved more often in the combination group (17 patients (33%) versus 13 patients (22%) respectively ($p=0.23$). In responders (n=48), defined as HBeAg negative at the end of follow-up, inflammation score improved in 65%, compared to 38% of non-responders ($n=0.06$). In conclusion, PEG-IFN therapy improves liver histology in CHB patients. We found an improvement in necroinflammatory scores but no significant reduction of fibrosis in both treatment groups.

Balancing Benefit and Burden in chronic hepatitis C: Recommendations on treatment continuation based on transaminase-levels and cost-per-cure

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Treatment for chronic hepatitis C induces side effects and costs, which can be limited if therapy is stopped in patients unlikely to respond.
In this meta-analysis we aimed to evaluate whether recommendations on treatment-continuation can be based upon low-cost and easily available transaminase-levels during treatment, taking into account the cost-per-cure.
Data of 1093 patients treated in 13 randomised trials with interferon alone or with ribavirin were analysed. Using multivariate logistic regression techniques, the increase in chance of sustained virological response (SVR) after prolongation of treatment from 24 to 48 weeks was calculated, depending on transaminase-levels at week 4 and week 12, on genotype and on baseline characteristics such as sex, age and the presence of cirrhosis. An increase in treatment efficacy was deemed clinically relevant if larger than 10%. If chance of SVR increased only with 5-10%, the cost-per-cure became decisive, with a limit of € 50,000 (equals € 25,000 per quality adjusted life year gained).
The increase in chance of SVR is smaller than 10% if treatment is continued up to 48 weeks in patients with genotype 1 or 4 without cirrhosis who have elevated transaminase-levels at week 4. The cost-per-cure for these patients would exceed € 50,000 using combination therapy. For cirrhotic patients, if treatment is continued up to 48 weeks, SVR rates increase with 14-47% depending on genotype and transaminase-levels at week 4. Non-cirrhotics with genotype 2 or 3 do not benefit from treatment continued beyond 24 weeks.
In conclusion, we present a promising new approach towards recommendations on treatment continuation, based upon dynamics of transaminase-levels and cost-effectiveness.

Management of spontaneuous hemorrhage and rupture of hepatocellular adenomas. Is it time for a change?

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Hepatocellular adenomas(HCA) may present with spontaneous hemorrhage and rupture, which can be life threatening. Our treatment policy consisted of stabilization and initial, conservative management, or in case of persistent bleeding, laparotomy and initial packing of the liver. Because of the assumed risk of malignant transformation of HCA, a delayed partial liver resection was undertaken after the bleeding episode. The aim of this study was to evaluate management of liver hemorrhage due to HCA and to assess a more expectant policy towards secondary resection.
Between May 1990 and August 2003, 17 female patients (pts) were diagnosed with acute hemorrhage and rupture of HCA (mean 34 years, range 23-48). 9 pts remained hemodynamically stable and could be treated conservatively. 1 pt with persistent intraabdominal bleeding underwent laparotomy and resection at first presentation, whereas 4 pts underwent laparotomy with initial packing of the liver. 13 pts eventually underwent secondary resection after a mean of 7 months (range 2-24). In most pts the preoperative CT-scans showed unspecific, partly hypo- and hyperdense lesions consistent with organized parenchymal hematoma. 3 pts were not operated after conservative treatment and showed no complications after a mean follow-up of 37 months (range 7-96). In one of these pts, the HCA showed regression from 5 to 1 cm after discontinuation of oral contraceptives. In 9 pts after elective resection, histopathological examination showed no specific tissue diagnosis. In 4 pts, 7 lesions microscopically compatible with HCA were identified (mean lesion size including area of previous hemorrhage 6.8 cm, range1.5-18 cm).
The absense of specific microscopical findings in the resection specimens of the majority of patients after management of acute hemorrhage of HCA in this series, casts doubts on the need for secondary liver resection. An expectant policy seems justified in these patients with regular follow-up imaging of the liver.

Circulating numbers of CD1d-restricted Natural Killer T cells in hepatitis C virus infected patients

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Natural Killer T (NKT) are characterized by co-expression of NK cell markers and a semi-invariant TCR and have been implicated to play an important immunoregulatory role by the rapid production of large amounts of Th1 and Th2 cytokines upon triggering. NKT cells are specifically activated by the glycolipid α-GalCer, which strongly suppresses hepatitis B viral replication in animal models via the production of IFN-α/β and IFN-γ. In a phase 1 clinical study in cancer patients, we found no signs of toxicity of α-GalCer and demonstrated that immunological responses were only observed in patients with relatively normal numbers of circulating NKT cells. Before studying the antiviral effects of α-GalCer in human HCV patients, we therefore set out to study the size of the human NKT cell population during HCV infection. Circulating NKT cell numbers in HCV infected patients were similar to those in healthy controls; patients with different HCV genotypes did not have statistically significant differences in NKT cell numbers. Furthermore, although we found that NKT cell numbers did not predict the occurrence of a virological response to HCV antiviral therapy, we did find a significant increase in circulating NKT cell numbers in patients with a virological response during antiviral treatment ($p=0.03$). Additional analyses on subgroups of patients are currently performed. Considering the potent pre-clinical antiviral effects of α-GalCer, our finding of normal circulating numbers of NKT cells during HCV infection is important since this opens the way to clinical trials with α-GalCer in HCV infected patients.

Early complications of radiofrequency ablation of liver tumours in the Netherlands

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Radiofrequency ablation (RFA) is a promising treatment for patients with unresectable liver metastases (LM) and hepatocellular carcinomas (HCC). Several clinical studies with large patient numbers have shown that local control of malignancies in the liver can be accomplished with RFA. In this study we report on early complications of the initial experiences with RFA in 8 medical centers in the Netherlands.
From 1999 through 2003, 108 patients treated with RFA were prospectively studied. Patients were deemed unsuitable for hepatic resection because of cirrhosis, bilobar disease, vascular proximity, previous hepatectomies or extrahepatic disease. Medical records were reviewed for demographics, characteristics of RFA procedure and follow-up data. Complications were divided into major (life threatening) and minor categories.
In 108 patients, 123 RFA procedures were performed. A total of 233 liver tumors (218 CRC and 15 HCCs) was treated with an average of 1.28 RFA applications per tumor. RFA was performed percutaneously (28 treatments, 23%) or during laparotomy (95 treatments, 77%). RFA was combined with partial hepatectomy in 32 procedures (34%). Two patients died within 30 days after RFA in combination with partial hepatectomy (mortality rate 1.8 %). Major complications occurred equally (8%) in percutaneous and open RFA and included bile duct injury (n=6), abdominal hemorrhage (n=2) requiring relaparotomy or transfusion, liver failure (n=2), fistula (n=2) and multi organ failure (n=1). Simultaneous partial hepatectomy was associated with increased major complication rate (19% vs 3%, $p<0.05$).
RFA can be safely applied for the local treatment of malignancies in the liver. However, initial complication and mortality rates in the Netherlands following RFA are considerable and are predominantly related to concomitant resection. These results show that RFA should be carried out in experienced hands as the treatment of complications may require extensive expertise.

Health Related Quality of Life of Chronic Liver Patients; A Survey in Dutch patients

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Since most studies on Health Related Quality of Life (HRQoL) of chronic liver patients were conducted in small clinical populations, there is still a need for a large study on HRQoL in chronic liver patients of various aetiology and disease stages that approaches a population-based study.
Eleven hundred and seventy-five members of the Dutch liver patient association completed the generic Short Form-36 and the disease-specific Liver Disease Symptom Index. We used multivariate linear, ordinal and logistic regression to put the HRQoL of transplanted patients, disease stages, aetiologies and viral hepatitis B and C into perspective with each other and with patients with diabetes mellitus and cancer.
All liver patients demonstrated a significantly reduced HRQoL compared to healthy controls, corrected for gender, age, education and marital status. Non-cirrhotic patients and compensated cirrhotic patients barely showed significant HRQoL differences. Transplanted patients demonstrated mostly a better HRQoL than non-cirrhotic and cirrhotic patients, although not as good as healthy controls. Hemochromatosis patients experienced significantly more bodily pain and a significantly worse role emotional functioning with increasing age than other aetiological groups. Hepatitis C patients without interferon therapy showed an impaired mental health than other chronic liver and non-liver patients. Interferon therapy aggravated this impaired mental health and additional aspects of HRQoL. The four elements that could lead to the poor mental health in hepatitis C patients were discussed.
In conclusion, this population-based study confirms the reduction in HRQoL in all liver patients and provides insight in the additional HRQoL reduction in patients with hemochromatosis and hepatitis C.

Regulatory T cells play a role in the persistence of hepatitis B virus infection

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Chronic hepatitis B virus (HBV) infection is characterized by a weak immune response to HBV. Since regulatory T cells (Tregs) are capable of suppressing the proliferation and the IFN-χ production of CD4+ T cells, Tregs could play an important role in this impaired T cell response. To investigate their role in chronic HBV the frequency and functionality of Tregs in peripheral blood of 42 patients and 21 healthy controls were compared.

The percentage of Tregs was determined using flowcytometry and specific antibodies. Tregs were identified as cells that stained positive for CD4, CD25, CD45RO and CTLA-4. The inhibition of the immune response against HBV antigens by Tregs was tested by depletion of the CD25+ cells using anti-CD25 MACS beads. CD25 depleted and non-depleted PBMCs from chronically infected patients were stimulated with HBV core antigen and after 6 days their proliferation was determined by incurporation of [^{3}H]-thymidine.

A higher percentage of Tregs was found within the population of CD4+ cells in peripheral blood of chronically HBV-infected patients compared to healthy controls (3.3% vs. 2.1%, p= 0.004). A significant correlation (Spearman's Rho of 0.861, p<0.001) was observed between the percentage of CD4+ cells that express CTLA-4 and the percentage of Tregs, but not between CD45RO expression or CD25 expression and Tregs. Depletion of the CD25+ cells from PBMCs of 2 chronic HBV infected patients results in an enhanced proliferation (32% and 148%) after stimulation with the HBV core antigen.

In conclusion, patients with a chronic HBV infection exhibit an increased percentage of Tregs in peripheral blood. These cells appear to have an HBV-specific suppressive effect, as was shown by depletion of CD25+ cells. The presence of Tregs capable of inhibiting the immune response against HBV might be an important mechanism by which tolerance is induced in chronic HBV patients.

ApoAV expression reduces plasma triglycerides in mice by reducing VLDL-triglyceride production and by stimulating lipoprotein lipase-mediated VLDL-triglyceride hydrolysis.

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ApoAV affects plasma triglyceride (TG) levels via an unknown mechanism. Adenovirus-mediated gene transfer of murine *apoa5* to C57/Bl6 mice resulted in a virus dose-dependent reduction (31-63%) of plasma TG levels. VLDL production was measured at the highest virus dose revealing comparable VLDL-apoB synthesis rates in control mice and mice overexpressing apoAV. Interestingly, the VLDL-TG production rate was diminished with 40% in the latter group of animals suggesting that apoAV interferes with hepatic apoB lipidation. The hypotriglyceridemic effect of apoAV could, thus, in part be explained by impaired VLDL-TG secretion. In addition, recombinant apoAV protein was found to significantly enhance lipoprotein lipase (LPL)-mediated TG hydrolysis from VLDL-like emulsions *in vitro*. Following an intragastric fat load, apoAV overexpressing mice showed complete absence of postprandial hypertriglyceridemia. Moreover, intravenously injected VLDL-like emulsions were cleared at an accelerated rate in apoAV overexpressing mice concomitant with increased uptake of emulsion-derived fatty acids by skeletal muscle and white adipose tissue. From these latter experiments, we conclude that apoAV is also a potent stimulator of LPL activity thereby stimulating hepatic clearance of remnant lipoproteins. In conclusion, apoAV expression reduces plasma TG levels in mice by reducing VLDL-TG production and by stimulating LPL-mediated VLDL-TG hydrolysis.

Differential effects of pharmacological LXR activation on peripheral and hepatic insulin sensitivity in lean and ob/ob mice

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Agonists for the nuclear liver X receptor (LXR) have been proposed as anti-diabetic drugs. However, treatment of mice with synthetic LXR ligands leads to hepatic steatosis which is supposedly associated with reduced hepatic insulin sensitivity. We addressed the apparent contradictory effects of LXR activation on hepatic and peripheral insulin sensitivity in a mouse model of type 2 diabetes, i.e. the ob/ob mouse. Lean and ob/ob mice were treated with the synthetic LXR agonist GW3965 and insulin sensitivity was assessed with hyperinsulinemic euglycemic clamps. Hepatic glucose production (HGP) and metabolic clearance rate (MCR) of glucose under clamped conditions were determined with [U-^{13}C]-glucose added to infused solutions. GW3965 treatment increased hepatic triglyceride content in lean (61.7 ± 7.2 vs. 12.1 ± 2.0 nmol/mg, $P<0.05$) and obese mice (221 ± 13 vs. 176 ± 19 nmol/mg, $P<0.05$). In lean mice, LXR activation did not affect glucose infusion rate (GIR) needed to maintain euglycemia, indicating unaffected whole-body insulin sensitivity. Hyperinsulinemia almost completely inhibited HGP (86 vs. 94% inhibiton, treated vs. control), in spite of hepatic steatosis in the treated mice. MCR was not affected by the agonist. In ob/ob mice, in contrast, LXR activation improved whole-body insulin sensitivity, as GIR was increased by 49% ($P<0.05$). As expected, hyperinsulinemia poorly inhibited HGP in ob/ob mice (42 vs. 28% inhibition, treated vs. control). LXR activation enhanced MCR (18.2 ± 1.0 vs. 14.3 ± 1.4 ml/kg/min, treated vs. control, $P=0.05$). Adipose mRNA levels of lipogenic genes (Srebp-1c, Glut4, Acc1 and Fas) normalised upon treatment in ob/ob mice. In conclusion, LXR activation improved peripheral insulin sensitivity in obese mice only. Reported anti-diabetic effects of LXR agonists in diabetic animals are therefore predominantly the result of a marginally improved peripheral glucose clearance and not of beneficial effects on hepatic glucose metabolism.

In vivo binding of transcription factors to the carbamoylphosphate-synthetase (CPS) glucocorticoid-response unit.

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Within the liver, the periportal and pericentral hepatocytes display functional complementarity. This is reflected by the gradients in expression of several enzymes. The CPS gene is used as paradigm to determine how periportal gradients in gene expression are established. At 6.3 kb upstream of the transcription-start site, a 100 bp enhancer mediates hepatocyte-specific, periportal, and hormone-inducible expression. Previous experiments have revealed it to contain a glucocorticoid-response unit (GRU). The GRU consists of a response element for the ubiquitous glucocorticoid receptor (GR), in combination with binding sites for the liver-enriched transcription factors HNF3 and C/EBP, and the unidentified factor P3. We aimed to determine whether the transcription factors are constitutively bound, and therefore need additional activation, or whether they bind only after hormonal stimulation.
To investigate the *in vivo* binding of transcription factors to the GRU, we used CPS-expressing FTO-2B hepatoma cells and CPS-negative Rat-1 fibroblasts. DNaseI-hypersensitivity analysis showed that the CPS enhancer has an open configuration in FTO-2B cells, whereas it is closed in Rat-1 fibroblasts. For high-resolution analysis we performed *in vivo* footprinting assays. With DNaseI, we located a specific hypersensitivity at the HNF3-binding sequence in FTO-2B, whereas protection was observed at the C/EBP and P3 binding sites. In Rat-1, protein binding was not detected. Subsequently, we demonstrated that the binding of HNF3, C/EBP, and P3 to their respective sites occurs in a hormone-independent manner. This may indicate that these factors have to be activated. For the visualisation of GR binding to the GRU we employed the same technique using DMS/piperidine for DNA cleavage. We found that GR binds to its response element only in FTO-2B cells and exclusively after treatment with glucocorticoids. This latter finding indicates that GR functions as the trigger for gene activation.

HNF4a binds Glutamine Synthetase upstream enhancer

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Glutamine Synthetase (GS), the enzyme that catalyses the ATP-dependent conversion of glutamate and ammonia into glutamine, is expressed in a tissue-specific and developmentally controlled manner. The focus of our interest is pericentral GS expression in the liver and our hypothesis is that more than one regulatory element is necessary for the proper pericentral GS expression.

Regulatory elements involved in the GS gene expression were delineated by transfection experiments in the FTO-2b cell line. It was found that 250bp long fragment, positioned about 2Kb upstream of the GS transcription start site, increases reporter gene expression. Its enhancer abilities are more pronounced in the presence of the GS first intron and 3'UTR sequences. The DNase I footprinting with the rat liver nuclear extract on the enhancer fragment revealed several hypersensitive sites and protected areas. MatInspector Professional recognized protected sequences as potential binding sites for several different transcriptional factors, one of which was the orphan nuclear receptor HNF4α.

The electrophoretic mobility shift assay showed that rat liver nuclear proteins bind with a very high affinity to our target sequence, yielding a large protein complex. Same results were obtained with the fragment that was 70bp long. In EMSA experiments, after treating the complex with HNF4α antibodies, we proved that this orphan nuclear receptor is a part of the protein complex.

Recently it was shown that GS is present throughout the liver in animals infected with an adenovirus conferring constitutive β-catenin expression. This finding implied that β-catenin is involved in the regulation of the pericentral expression of the GS gene. The supershift experiment on the 70bp fragment with β-catenin antibodies proved that the β-catenin is also present in the protein complex.

Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal origin

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Background: Peritoneal carcinomatosis (PC) due to colorectal cancer (CRC) is the 2nd most frequent cuse of death after metastatic disease to the liver. In ±25% of patients no other metastatic ecept PC is present. Prognosis after conventional surgery and chemotherapy is about 6 months. Uncontrolled phase II studies suggest that aggressive surgical cytoreduction (SCR) combined with hyperthermic intraperitoneal chemo-therapy (HIPEC) can result in ±25% long-term disease-free survival.
Aim of the study: Confirm in a randomized phase III study that aggressive SCR plus HIPEC leads to increased long-term survival in PC due to CRC. Description of morbidity of the procedure and prognostic factors.
Results: In 1998-2001 a single center randomized study was done in 106 patients, median age 55 year, 58 were male. Presentation of PC and CRC was synchronous in 58 and metachronic in 47. Primary site was appendix in 18, colon in 75 and rectum in 12. After a median follow-up of 22 months, median survival was 12.6 months in the standard arm and 22.3 months in the experimental arm (p=0.032). Treatment related mortality was 8%. Most complications from HIPEC were related to bowel leakage. The abdomen was divided in 7 regions. If 0-5 regions were involved, survival was significantly better (n=median > 29 months) compared to 6-7 regions involved by PC (median 5 months) (p<0.0001). If SCR was macro-scopically complete (n=18, R1), median survial was significantly better than in patients with limited residual disease (n=21, Ø<2.5 mm, R2a) or gross residual disease (n=10, R2b) (p<0.0001).
Median hospital stay in the experimental group was 29 days, duration of laparotomy 485 minutes, median blood loss 3.9 L. An average of 1.8 visceral resections was performed. Fistulas occurred in 7 patients.
Conclusions: Surgical cytoreduction plus HIPEC improves survival in PC du to CRC. Patients with 6-7 involved areas or if gross residual disease is present after SCR do not benefit from the procedure.

Small gallbladders stones, good gallbladder motility and fast crystallization are major risk factors for acute pancreatitis

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Acute pancreatitis is the most severe complication of gallstone disease. We studied the role of crystallization, bile composition, gallbladder motility, and numbers or sizes of gallstones in the pathogenesis of acute pancreatitis. Methods: We measured gallbladder emptying by ultrasonography in patients recovered from acute biliary pancreatitis (N=18) and in patients with uncomplicated gallstone disease (N=30). Numbers and sizes of gallstones, bile composition and crystal observation time were determined after subsequent cholecystectomy. Results: Gallbladder emptying was much stronger in patients with pancreatitis than in those with uncomplicated disease (minimal postprandial volumes: 5.4±1.0 vs 8.4±0.7 mL, P = 0.001). Patients with pancreatitis had smaller gallstones than patients with uncomplicated disease (smallest stone diameters: 2±1 vs 8±2 mm, P = 0.009). Also, crystallization occurred much faster in bile of patients with pancreatitis (1.0±0.0 vs 2.5±0.4 days, P = 0.005), possibly due to higher mucin concentrations (3.4±2.0 vs 0.7±0.2 mg/mL, P = 0.02). On the other hand, no significant differences were found in number of gallbladder stones, total or individual biliary lipid concentrations, phospholipid/(bile salt + phospholipid) ratio, cholesterol saturation index, bile salt species, phospholipid classes, total proteins or IgG, IgM, IgA, haptoglobin and α-1 acid glycoprotein.
Conclusions: Small gallbladders stones, good gallbladder motility and fast crystallization are major risk factors for acute pancreatitis.

Peptic ulcer bleeding, NSAID use and Helicobacter pylori infection; a prospective study evaluating incidence, prevalence and outcome

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Peptic ulcer bleeding is still a major health problem. Prevention of ulcer bleeding is important. Concomitant use of proton pump inhibitors with NSAIDs or eradication of H. pylori may reduce peptic ulcer bleeding. A prospective study was conducted to determine prevalence of NSAID use and H. pylori infection in peptic ulcer bleeding patients.
In 2000, data of all patients presenting with peptic ulcer bleeding were prospectively collected in a defined area, including 14 hospitals and a catch area of 1.68 million people. Data collection included co-morbidity, NSAIDs and acid suppressive therapy, H. pylori status and eradication therapy, rebleeding and mortality. Follow up data was collected after a mean of 31 months.
361 patients presented with ulcer bleeding, giving an incidence of 21.5 cases per 100 000 persons per year. Mean age was 71 years, 41% had severe or life threatening co-morbidity. NSAIDs were used by 52%, and in only 17% concomitant acid suppressive therapy was given. H. pylori infection was tested in 64%. Of the patients tested for H. pylori 43% was positive. Twenty-three percent was H. pylori negative and not using NSAIDs. Of the H. pylori positive patients, 89% received eradication therapy. Rebleeding during initial admission occurred in 19% of the patients and mortality was 14%. During follow up recurrence of acute upper gastrointestinal bleeding occurred in 2.5% and mortality was 30%.
Conclusions: Half of all ulcer bleeding was associated with NSAID use. Only a minority of NSAID-users also used concomitant acid suppressive therapy. Helicobacter pylori is still not assessed systematically in all patients with ulcer bleeding and if positive not everyone received eradication therapy. Almost a quarter of the ulcers were neither associated with H. pylori nor NSAID use. Rebleeding during hospitalisation and mortality, both during hospitalisation and follow up, were substantial.

Molecular Aberrations are Still Present after Ablative Therapy of Barrett's Esophagus

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Both photochemical and thermal methods are used for ablation of Barrett's esophagus (BE). We assessed whether 5-aminolevulinic acid based photodynamic therapy (ALA-PDT) and/or argon plasma coagulation (APC) were able to eliminate pre-existent molecular aberrations in BE.
Thirty (24M/6F) patients with a mean BE length of 4 cm (range, 2-8) with no (n=14), low-grade (LGD; n=8) or high-grade dysplasia (HGD; n=8) were treated with ALA-PDT (60 mg/kg ALA; 633 nm; n=6), APC (65 W; n=10) or ALA-PDT plus APC (n=14) until no macroscopic BE was detectable. Patients were evaluated at 3-months intervals and after 1 year at 6-months intervals (mean follow-up: 20 months, range, 6-36). Biopsies were evaluated for intestinal metaplasia or dysplasia. The proliferation index (PI) was estimated by Ki-67 immunohistochemistry with Mib-1 (increased if PI >20), overexpression of p53 protein was measured by immunostaining with the antibody DO-7 (abnormal if >15% of nuclei were positive). The ploidy status was assessed by DNA in situ hybridization with a probe for chromosome 1.
Complete removal of BE was achieved in 22/29 (76%) patients. During follow-up, non-dysplastic BE was detected in 5 patients, LGD in 1 patient and HGD in 1 patient. In 4 patients (including 1 LGD), BE was found underneath squamous epithelium, and in 3 patients (including 1 HGD), next to regenerated squamous epithelium. Before treatment, p53 overexpression was present in 8/25 (32%), PI was increased in 24/25 (96%), and hyperploidy was present in 14/22 (64%) patients. An increased PI was found in 4/5 (80%) patients with non-dysplastic BE during follow-up. In the patient with LGD both p53 overexpression and hyperploidy were present, whereas in the patient with HGD p53 was overexpressed during follow-up.
Conclusion: Molecular aberrations are still present in BE detected after ablative therapy. Endoscopic treatment of BE should therefore aim at persistent complete elimination of all Barrett's metaplastic tissue.

Narrow-band Imaging (NBI) in Barrett Esophagus (BE): What Features Are Relevant for The Detection of High-grade Dysplasia (HGD) and Early Cancer (EC)?

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NBI is a new endoscopic technique, which is based on a RGB-sequential endoscopy system with narrowed band-pass-ranges of the RGB rotary filters and increased relative contribution of the blue band-pass filter. As a result, NBI enables detailed inspection of the mucosal and vascular surface patterns with high resolution and contrast, without the use of staining agents. Our aim was to find and validate descriptive factors in the NBI images that may predict HGD/EC in BE. 28 patients with BE (11 surveillance, 11 work-up for HGD/EC, 6 follow-up after endoscopic treatment; mean length BE: 5.3 cm)were investigated with a prototype NBI-system (Olympus Tokyo, Japan), which has a HR-videoendoscope and two imaging modes: a standard HR-mode and a HR-NBI-mode with the possibility of easy switching between both modes. 100 NBI images with corresponding histological correlation were available. Based on the literature and an unblinded evaluation of 10 images, a set of 15 possible descriptive factors relating to the mucosal (6) and vascular (9) patterns was constructed, according to which 30 images ("learning set") were evaluated in consensus by two experienced endoscopists, who were blinded to histopathology. Multivariate analysis was performed to correlate descriptive factors to the presence of HGD and/or EC. Only the presence of an irregular mucosal pattern ($p=0.039$) and the presence of an irregular vascular pattern ($p=0.025$) were found to be independent predictors of HGD/EC. Nodularity and description of the type of mucosal or vascular patterns did not predict HGD/EC.
Conclusions: The preliminary results of this ongoing study suggest that a "regular versus irregular model" for both mucosal and vascular patterns may be more important in detecting early neoplasia in BE than a "pattern classification model". Blind assessment of relevant descriptive factors in an independent set of images as well as intra-/inter observer studies are currently being performed.

The First Experience with Video Autofluorescence Endoscopy (AFE) for The Detection of High Grade Dysplasia and Early Cancer (HGD/EC) in Barrett Esophagus (BE)

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Autofluorescence (AF) imaging may improve the detection of HGD/EC in BE. Currently available AFE systems incorporate only the green/red AF in the AF-images and produce inferior quality of white light (WL) images due to the use of fiber optic endoscopes. We report on the use of an AFE system with two high-quality CCD chips: one for WL-endoscopy (WLE) and one for integration of total AF (after blue light excitation) plus green and red reflectance into a real-time pseudocolor AFE image. 22 patients with BE (6 surveillance, 9 work-up for HGD/EC, 7 follow-up after endoscopic therapy; mean length BE 5.9 cm) were investigated with a prototype video-AF-WL system (Olympus, Tokyo, Japan), which has a sequential RGB light source and a high-resolution video-endoscope with separate CCD chips for WLE and AFE. During endoscopy, the BE was first screened with WLE for visible lesions followed by AFE for detection of additional lesions. Non-dysplastic BE (NDBE) appeared green on AFE and suspicious areas were blue to violet. All suspicious lesions, and control areas that appeared normal on AFE were sampled for histopathology. Biopsies were evaluated by an expert pathologist blinded to the endoscopic findings. 12 of the 22 patients had one or more areas with HGD or EC. With WLE, areas with HGD/EC were detected in 10 patients. Additional areas with HGD/EC, occult with WLE, were detected in 6 patients. In 2 of these patients, no suspicious lesions were identified by WLE and the areas with HGD/EC detected with AFE were only identified based on their suspicious AFE color. In total, 21 additional suspicious lesions detected with AFE were sampled; of these 7 were HGD/EC. From the 17 non-suspicious samples only 1 was HGD.
Conclusion: This uncontrolled study suggests that this 2-CCD video-AF-WL system increases the detection of HGD/EC in BE. Non-dysplastic mucosa with reactive changes and areas classified as indefinite for dysplasia may also appear abnormal on AFE.

Clinical implications of videocapsule endoscopy; 1-year follow-up

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Videocapsule endoscopy (VCE) is a new tool to investigate the small bowel. Main indications are anaemia due to gastrointestinal blood loss and suspected Crohn's disease of the small bowel. Diagnostic yield of VCE is high. However, there is little information about clinical consequences and outcome of a diagnosis established by VCE.
In this study the clinical consequences of VCE findings were assessed.
One year after VCE was performed, a questionnaire was sent to the referring physicians. Clinical implications were classified in 6 groups: change of medication, endoscopic intervention, surgical procedures, avoiding other procedures, supporting current policy or no clinical consequences. Changes in overall clinical condition in the year following VCE were evaluated. In patients who underwent VCE for obscure bleeding, haemoglobin level at the time of VCE and after one year were compared by paired t-test.
37 Questionnaires were sent and 30 (81%) were returned. Main indications were obscure gastrointestinal bleeding (n=22, 73%) and suspected Crohn's disease (n=6, 20%). Diagnostic yield was high with a definite diagnosis in 33% and a possible diagnosis in 37%. Results of VCE led to a change in medication in 8 patients (26.7%), to endoscopic intervention in 1 patient (3.3%) and to a surgical procedure in 2 patients (6.7%). Other procedures were avoided in 4 patients (13.3%) and current policy was supported in 7 patients (23.3%). In 8 patients (26.7%) VCE had no clinical impact. Clinical condition of 17 patients (56.6%) improved in the year following VCE. The obscure GI bleeding group showed an increase of the mean hemoglobin level from 6.8±1.1 (SD) to 7.7±1.5 mmol/l ($p=0.02$). All referring physicians would again perform a VCE for the same indications in the future.
Conclusion: VCE is a non-invasive tool for investigation of the small bowel with a high diagnostic yield leading to relevant clinical implications in 50 % and supporting current policy in 23% of patients.

MnSOD gene polymorphism predisposes to the development of gastroesophageal reflux disease

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Twin studies have suggested that the observed familial aggregation of gastroesophageal reflux symptoms has a genetic component. Chronic inflammation in patients with gastroesophageal reflux disease (GERD) is associated with increased levels of lipid peroxidation and as such polymorphisms in antioxidant genes may predispose to the development of GERD. In this study, we investigated whether polymorphisms in genes involved in the protection against oxidative stress-related damage were associated with the development of GERD.
The allelic variation of superoxide dismutase (MnSOD; Ala9Val), catalase (CAT; –262C→T), glutathione S-transferases M1 (GSTM1; deletion), T1 (GSTT1, deletion), P1 (GSTP1; 1404A→G and 2294C→T) and 8-oxoguanine DNA glycosylase (OGG1; Ser326Cys) were determined in Caucasian patients (n=292)with endoscopically confirmed GERD, consisting of patients with Barrett's esophagus (BE; intestinal metaplasia; n=192) and reflux esophagitis (RE; n=100), by PCR-RFLP and multiplex SNaP-shot™ methods. Genotype frequencies were compared to European Caucasian controls (n=987).
Overall, the allele frequencies of CAT, GSTM1, GSTT1, GSTP1 and OGG1 genotypes did not differ between GERD patients and controls, and also not between BE and RE patients. However, the allelic distribution of the MnSOD genotypes differed significantly between GERD patients and controls with the homozygous MnSOD ala-allele (CC) being more prevalent in patients with GERD than in controls (p=0.041). Within the GERD population, the prevalence of the MnSOD ala-allele was similar between BE and RE patients.
Conclusion: The MnSOD Ala9Val gene polymorphism is associated with GERD in a Caucasian patient population. Increased individual oxidative stress susceptibility as a consequence of MnSOD gene polymorphisms may predispose patients with gastroesophageal reflux to the development of reflux esophagitis and BE.

Long mucin 6 alleles are associated with increased susceptibility to Helicobacter pylori infection

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H. pylori resides in the mucus gel layer of the stomach. The main constituents of this layer are high molecular weight glycoproteins named mucins. The genes encoding for these mucins show a variable number tandem repeat (VNTR) polymorphism resulting in polypeptides that substantially differ in length and glycosilation. These differences in mucin structure influence their protective properties and may therefore be related to susceptibility to *H. pylori* infection. Aim of this study was to investigate the relationship between mucin 6 (MUC6) allele length and *H. pylori* infection.

Blood samples were collected from patients referred by their general physicians for *H. pylori* ^{14}C urea breath testing. MUC6 allele lengths were determined by Southern blot analysis. The relationship between MUC6 allele length and *H. pylori* infection was analyzed by means of logistic regression and adjusted for patient characteristics.

MUC6 allele lengths were determined in 60 patients, of whom 40 patients were infected with *H. pylori.* MUC6 was found to be highly polymorphic, with P*vu*II-restricted allele lengths ranging from 8 to 19 kbp. Patients with one or two long alleles (>13.0 kbp) had a higher risk of being infected with *H. pylori* than patients with two short alleles (78% vs. 54%, $p<0.05$, adjusted odds ratio 5.54, 95%CI (1.4-21.7).

Conclusions: Long MUC6 alleles are associated with increased susceptibility to *H. pylori* infection.

Host factors, IL1B-511 & IL-1RN gene polymorphisms, and bacterial factors of Helicobacter pylori, cagA and vacA subtypes, in peptic ulcer disease and non ulcer dyspepsia: a synergistic effect

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Introduction: Environmental, bacterial and host factors are linked to the susceptibility, severity and clinical outcome of infectious diseases. Disease associated bacterial loci have been identified in *Helicobacter pylori*, among them the polymorphic gene encoding cytotoxin (*vacA*) and the cytotoxin associated gene A (*cagA*). Both bacterial factors are associated with peptic ulcer disease (PUD). In addition, specific polymorphism of interleukin-1B promoter region (*IL1B–511*) and interleukin-1 receptor antagonist gene (*IL-1RN*) of the host also appear to be associated with PUD in *H. pylori* infected persons.
Aim: To determine the interrelationship between the genotype of *IL1B–511* and *IL-1RN* gene of the host, the *H. pylori* factors *cag*A status and *vacA* subtype and the clinical outcome in *H. pylori* related diseases, both by single trait and carrier trait analyses.
Methods: Ninety Dutch Caucasian consecutive patients, 43 diagnosed with PUD and 47 had non ulcer dyspepsia (NUD), were included into the study. The *H. pylori cagA* and *vacA* status was determined using PCR and/or serology. DNA was isolated from sera to analyse *IL1B–511* and *IL-1RN* gene polymorphisms.
Results: All genotypes for the IL1 cluster genes were in Hardy-Weinberg equilibrium showing Mendelian inheritance. NUD vs PUD (p-value; OR): 1) *IL1B-511* allele 2 (*2): 56% vs 62% (0.5; 1.4); 2) *IL1RN*2*: 28% vs 43% (0.19; 1.9); 3) *cag*A+: 67% vs 91% (0.0073; 5.2); 4) *vac*A s1+ partially determined (in progress) for 25 NUD and 20 PUD patients: 12% vs 30% (0.45; 2.4). Carrier trait analyses NUD (25 patients) vs PUD (20 patients): 1) *IL1B*2/IL1RN*2*: 14% vs 30% (0.13; 2.5); 2) *IL1B*2/IL1RN*2/cag*A+: 5% vs 26% (0.008; 7.0); 3) *IL1B*2/IL1RN*2/cag*A+/*vac*As1+: 4% vs 30% (0.034; 10.2).
Conclusions: *cagA* is associated with the more severe clinical outcome PUD in *H. pylori* infected patients. Carrier trait analyses showed that combining these bacterial and host factors provides the strongest risk profile, increasing ORs from 1.4 to 10.2.

Molecular Characterization of Hepatocystin, the Protein that is Defective in Autosomal Dominant Polycystic Liver Disease

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Autosomal dominant polycystic liver disease (PCLD) is characterized by the presence of numerous cysts spread throughout the liver parenchyma. Recently, we discovered that PCLD is caused by mutations in a protein named hepatocystin. Genetic analyses of PCLD patients have so far identified nine different mutations in hepatocystin, all predicted to cause premature chain termination. The cellular function of this protein, however, remains unclear. As a major step towards elucidating the involvement of hepatocystin in PCLD, we have undertaken a biochemical and morphological characterization of both normal and mutant forms of hepatocystin. The results of our studies indicate that normal hepatocystin is an endoplasmic reticulum (ER) protein that associates with the catalytic alpha subunit of glucosidase-II. The 1338-2 A>G truncating mutation observed in some PCLD patients produces a protein that is not retained in the ER but secreted into the medium, and that does not assemble with the glucosidase-II alpha subunit. As a consequence, mutant hepatocystin is undetectable in PCLD liver tissue. Further, liver and Epstein-Barr-Virus-transformed lymphocytes from the patients contain reduced levels of both normal hepatocystin and glucosidase-II alpha subunit. These findings are most consistent with a role of hepatocystin in carbohydrate processing and quality control of newly synthesized proteins in the ER. Therefore, reduced ER processing of some key regulator of cell proliferation may underlie PCLD.

Non-absorbable fat enhances the fecal excretion of 2,2',4,4'-tetrabromodiphenyl ether (BDE-47) in rats by interruption of its enterohepatic circulation.

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Polybrominated Diphenyl Ethers (PBDEs) are lipophilic compounds used on a wide scale as flame retardants. PBDEs accumulate in the body and are thought to have similar negative effects on human health as dioxins. Disposal of PBDEs from the body is slow and only occurs to an appreciable extent during lactation. We hypothesized that increased fecal fat excretion could enhance fecal PBDE disposal through hydrophobic association in the intestinal lumen. BDE-47 was used as a PBDE model compound because of its high level in environment and subsequent human exposure.
Male Wistar rats were fed a chow diet with 35 energy% fat, mimicking that of a human Western diet. At day 17, ^{14}C-labeled BDE-47 was administered to rats by intragastric gavage. From day 21, rats were divided in a control group, continuing on the same diet, and in an experimental group, fed a high-fat diet supplemented with sucrose polyester, a non-absorbable lipid that is excreted via the feces in unmetabolized form. Feces was collected from day 21 – 42. At day 42, bile was collected and the ^{14}C content of feces, bile and organs was measured. Sucrose polyester treatment increased fecal excretion rates of fat (+83%, $p<0.02$) and ^{14}C-BDE (+175%, $p<0.001$). Fecal ^{14}C-BDE excretion appeared strongly correlated with fecal fat excretion ($r=0.77$, $p<0.04$). Based on biliary and fecal ^{14}C-BDE-47 secretion rates it could be calculated that sucrose polyester treatment decreased the net intestinal reabsorption of ^{14}C-BDE-47 from 76% to 11% of the amount excreted into the bile.
Conclusions: Sucrose polyester treatment in rats enhances fecal excretion of BDE-47 through interruption of its enterohepatic circulation. This strategy could be useful for humans to decrease the body burden of these and related hydrophobic compounds, such as dioxins and polychlorinated biphenyls (PCBs).

NOD2 mediates anti-inflammatory signals induced by TLR2 ligands: implications for Crohn's disease

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Mutations of the *NOD2/Card15* gene have been associated with an increased susceptibility to Crohn's disease, but the mechanisms mediated by *NOD2* remain elusive. The aim of the present study was to investigate the functional consequences of the 3020insC frameshift mutation of *NOD2/Card15* gene. In Crohn's disease patients, homozygous for the frameshift mutation, wild type patients and healthy controls, pro- and anti-inflammatory cytokine production was studied after stimulation with various bacterial ligands, which interact either with the pattern recognition receptors Toll-like receptor-4 (TLR4) or TLR2. In the present study, we demonstrate that the 3020insC frameshift mutation results in defective release of interleukin-10 and transforming growth-factor-β from blood mononuclear cells after stimulation with the Toll-like receptor (TLR)2 ligands peptidoglycan and Pam3Cys-KKKK, but not with bacterial lipopolysaccharide, a TLR4 ligand. This suggests an involvement of *NOD2* in the signalling pathway of TLR2. The potential significance of this finding in patients with Crohn's disease homozygous for this *NOD2* mutation was substantiated by the finding of decreased anti-inflammatory cytokine release when cells of these patients were stimulated with *Bacteroides* species, an enteric microorganism implicated in the pathogenesis of Crohn's disease. In conclusion, these data imply that defective IL-10 and TGFβ production by mononuclear cells in patients bearing loss-of-function mutations of *NOD2* represents a novel pathogenetic mechanism in Crohn's disease.

IFN-γ mediated epithelial barrier disruption involves claudin-2 cleavage

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Enhanced intestinal permeability is associated with the pathology of inflammatory bowel disease (IBD). The diminished barrier function as often found in these patients is associated with loss of tight junction strands and organisation. Enhanced production of inflammatory mediators, e.g. IFN-γ can be found in the mucosa of IBD patients. *In vitro* studies have shown IFN- γ to affect the tight junction proteins ZO-1 and occludin. Since claudins are main constituents of tight junctions this prompted us to study the effects of IFN- γ on claudin expression in relation to intestinal epithelial permeability. T84 cells were grown until 2 weeks postconfluency in transwell culture plates followed by incubation with IFN-γ . for 72h. Barrier function (n=5) was determined by measuring transepithelial resistance (TER; ohm.cm^2) and permeability (HRP and 4 kD FITC-dextran flux; pmol/cm^2/h). Claudin-1, -2, -3, -4 and occludin expression was determined by western blotting. Claudin-2 and occludin were markedly reduced after IFN-γ incubation which correlated with decrease of TER (t=72h, 1426 ± 89 (control) vs 621 ± 34 (100 U/ml IFN- γ), $p<0.001$) and increased HRP fluxes (0.2 ± 0.1 vs 2.8 ± 0.7, $p<0.05$). Claudin-1, -3, and -4 were not affected. Cycloheximide prevented IFN-γ mediated decrease in TER and occludin expression while degradation of claudin-2 was not affected. Protease inhibitor AEBSF abolished IFN-γ mediated barrier disruption which correlated with upregulation of claudin-2 expression.
Conclusion: IFN-γ induced loss of TER and increased permeability is accompanied by decreased expression of tight junction proteins claudin-2 and occludin. The IFN-γ effect on occludin was mediated via de novo protein synthesis while a serine protease inhibitor prevented barrier disruption by increasing claudin-2 expression.

The presence of the cag Pathogenicity Island is associated with increased ros scavenging by helicobacter pylori

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Helicobacter pylori infection is a risk factor for the development of gastric carcinoma. Reactive oxygen species (ROS) are thought to play an important role in tumor induction, and *H. pylori*-positive patients show increased levels of ROS in the gastric mucosa. *H. pylori* protects itself from the harmful effects of inflammation induced ROS by its ROS scavenging enzymes SOD and catalase. *cag*- positive (*cag*+) *H. pylori* strains induce a stronger inflammatory response than *cag*- negative (*cag*-) strains, and probably require a more active ROS scavenging system. The aim of this study was therefore to compare ROS scavenging capacity between *cag*+ and *cag*- strains.
ROS scavenging activity was determined in the presence of the superoxide-producing xanthine/xanthine oxidase system (XOS) to overnight cultures of *H. pylori*, and superoxide levels were measured on a Bruker electron spin resonance spectrometer in combination with spin-trapping techniques. Decrease in dimethyl-1-pyrroline-N-oxide spin-trapped radical peak surfaces was determined as a measure for ROS scavenging activity. Differences were tested using the Mann Whitney U-test, and considered significant if $p<0.05$.
ROS was only produced when XOS was added to the culture medium, and were characterized by a superoxide radical signal peak surface. Levels of ROS were 68.3 ± 2.3 in medium, and decreased significantly when *cag*- and *cag*+ *H. pylori* strains were added to the medium (47.2 ± 4.0, $p=0.013$ and 33.0 ± 3.8, $p=0.003$, respectively). *cag*+ strains show an higher ROS scavenging capacity than *cag*- strains ($p=0.014$). When *H. pylori* strains were heat or formaldehyde inactivated, no radical scavenging activity was seen.
H. pylori strains actively scavenge ROS, with *cag*+ strains being better radical scavengers than *cag*- strains. This is likely to be an adaptive response of *cag*+ *H. pylori* strains to the increased levels of ROS in the inflamed gastric mucosa, and may play an important role in chronic colonization by *H. pylori*.

Analysis of Functional Interleukin-12 Gene Polymorphisms in the Susceptibility to Crohn's Disease

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Interleukin-12 (IL-12) is a key cytokine involved in the immune response and consists of 2 subunits: IL-12p40 *(IL12B)* and IL-12p35 (*IL12A)*. Increased levels are found in the lamina propria of patients with Crohn's disease (CD) and blocking this cytokine has been proposed as a therapeutic option. Gene polymorphisms in *IL12B* were previously found to be associated with susceptibility to multiple sclerosis, asthma and type I diabetes. We and others demonstrated that these polymorphisms affect the expression of IL-12 *in vitro*. Genetic variation in *IL12B* might therefore, through their effect on IL-12 synthesis, play a role in the susceptibility to CD. In the current study we searched for additional polymorphism in *IL12B* and determined their involvement in the susceptibility to CD in a large number of families with at least one affected child.
DNA derived from 6 high (>300pg/ml) and 6 low (<50pg/ml) secretors of IL-12 was analysed for polymorphisms in *IL12B* using single-strand conformational polymorphism analysis and direct sequencing. 305 families with CD were genotyped using the intrafamilial transmission disequilibrium test and by case control analysis involving 520 controls.
A novel single nucleotide polymorphism in the 5'UTR of *IL12B* was found. Genotype and haplotype analysis of this polymorphism as well as two previously described polymorphisms did not reveal an association with the susceptibility to CD. In addition, stratification for *CARD15* status did not affect the results.
The low genetic variation in *IL12B* indicates a high level of conservation, consistent with the key regulatory role of this cytokine. The lack of association with susceptibility to CD, both by case-control analysis as well as by intra-familial analysis in a large cohort of patients, makes a direct involvement of this gene unlikely. However, confirmation in an independent cohort is warranted. Further studies to identify the factors that drive the aberrant IL-12 expression in CD are necessary.

The rotavirus enterotoxin NSP4 interacts with intestinal basement membrane proteins

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The rotavirus nonstructural protein-4 (NSP4) acts as an enterotoxin causing age-dependent diarrhea in young mice. NSP4, when administered to intestinal cells, is able to induce chloride secretion via a yet unknown signal transduction pathway. This study aims to clone and identify cellular proteins interacting with NSP4 in order to gain more insight into RV pathogenesis. To identify cellular proteins that interact with NSP4, a yeast two-hybrid screening was carried out using an intestinal cDNA library derived from Caco-2 cells. Caco-2 cells have enterocyte-like characteristics and are susceptible to rotavirus infection. The two-hybrid screening resulted in the identification of two proteins, laminin-beta-3 and fibronectin, which bound to NSP4. These interactions were confirmed by co-immunoprecipitation experiments using anti-NSP4 antibodies and homogenates of infected Caco-2 cells. Furthermore, in small intestinal tissue sections of mice infected with a murine rotavirus strain (EDIM), we have demonstrated by immunohistochemistry that NSP4 was not only detectable in infected enterocytes at the tips of the villi but also co-localized with the basement membrane proteins laminin-beta-3 and fibronectin. Deletion analysis indicated that the amino acid region 87-145 of NSP4 binds to fibronectin and laminin-beta-3. Conclusions: The enterotoxin NSP4 binds to the basement membrane proteins laminin-beta-3 and fibronectin, which indicates that NSP4 is released basolaterally from infected enterocytes.

Inhibition of JNK MAPK activity improves epithelial barrier integrity

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Increased intestinal permeability is thought to play an important role in the immunopathogenesis of Crohn's disease. Inflammatory cytokines, e.g. IFN-γ are often studied for their capacities to induce barrier disruption. Little is known about the role of signaling molecules like mitogen activated protein kinases (MAPK) in intestinal epithelial cells following cytokine stimulation. We investigated the importance of the phosphoinositide-3-kinase (PI3K), MAPK, and protein kinase C (PKC) pathways in regulation of epithelial barrier integrity. T84 monolayers were incubated with selective inhibitors for PI3K (LY294002, 10 μM), MAPK (ERK (PD98095, 5 μM), p38 (SB203580, 1 μM) and JNK (SP600125, 20 μM), and PKC (rottlerin, 5 μM) or the flavonol quercetin (25 μg/ml) in the presence or absence of IFN-γ (100 U/ml). Both trans-epithelial resistance (TER) and 4kDa-FITC-dextran fluxes were measured to evaluate barrier integrity. Moreover, STAT1 phosphorylation was determined by western blotting. T84 monolayers developed adequate barrier integrity with high resistance and low dextran fluxes in the basal conditions. These barrier properties were dramatically affected during incubation with IFN-γ for 72h, which caused reduced resistance (1484 ± 86 vs 790 ± 44 ohm.cm^2, $p<0.002$) and increased dextran fluxes (20 ± 11 vs 520 ± 60 pmol/cm^2/h). Inhibition of JNK MAPK in particular, dramatically enhanced basal resistance and reduced the IFN-γ mediated permeability for over 50% ($p<0.02$). The flavonol quercetin, similar to the PI3K inhibitor, ameliorated IFN-γ mediated barrier disruption and inhibited IFN-γ induced STAT1 phosphorylation (n=3). In contrast, PKC inhibition only marginally affected basal resistance and aggravated IFN-γ mediated barrier disruption. Conclusion. JNK MAPK may play an essential role in the regulation of epithelial barrier function and is an interesting therapeutic target in diseases with underlying intestinal barrier defects.

Multidrug Resistance Protein (MDR1) is decreased in inflamed intestinal epithelium in inflammatory bowel disease

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Background: The Multidrug Resistance Protein (MDR1) is a drug efflux pump at the apical surface of epithelial cells. Recent studies show that mdr1a deficient mice develop spontaneous colitis, suggesting a role of MDR1 in the pathogenesis of inflammatory bowel disease (IBD).
Aim: To study (1) the distribution of MDR1 in the human intestine and (2) the regulation of MDR1 in active IBD.
Methods: Using immunohistochemistry and real time RT-PCR, we studied MDR1 and iNOS expression in mucosal biopsies from the ileum and colon of IBD patients (10) and healthy subjects (5). Biopsies were obtained from inflamed and non-inflamed mucosa.
Results: In normal human ileum and colon, a strong apical MDR1 staining of the epithelium was observed and occasionally also the upper part of the crypts stained positive. MDR1 mRNA levels were approximately 7-fold higher in the ileum compared to the colon. Epithelial staining was continuous in the ileum and patchy in the colon. MDR1 expression in proximal and distal colon was equal. MDR1 expression in non-inflamed intestinal tissue from IBD patients and normal controls was comparable. MDR1 protein and mRNA levels in mucosa from inflamed parts of the intestine showed a decreased MDR1 protein and mRNA expression, this was inflammation grade dependent and was inversely correlated to iNOS expression.
Conclusion: In healthy tissue, MDR1 expression is most prominent in the ileum compared to the colon, with equal distribution throughout the colon. We observed a strong decrease of MDR1 expression in inflamed parts of the intestine of IBD patients. Low MDR1 expression in IBD (1) may be an adaptive response and may modulate the inflammation; (2) may increase drug efficacy due to decreased elimination of drugs from the intestinal mucosa.

Air swallowing, intragastric air and gaseous and liquid gastro-esophageal reflux: a study using multiple intraluminal impedance

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With every swallow a certain amount of air is transported to the stomach. The stomach can protect itself from excessive distention through venting of gas. This is accomplished through transient relaxations of the lower esophageal sphincter, which is also one of the mechanisms underlying liquid gastroesophageal reflux. The aim of this study was to investigate whether swallowing of air leads to an increase of the size of the intragastric air bubble and to gaseous and liquid gastroesophageal reflux. Multichannel intraluminal electrical impedance measurement was used to quantify the incidence of swallowing of air in 20 healthy volunteers before and after a meal. The size of the intragastric air bubble was measured by means of fluoroscopy. Gastroesophageal reflux was assessed by impedance and pH measurements. The total number of air swallows (21.3 ± 3.7 vs 24.8 ± 2.9 / h) and gas reflux episodes (4.6 ± 1.0 vs 3.0 ± 0.6 / h) did not differ significantly between the pre- and postprandial recording period. In contrast, the incidence of liquid reflux (0.6 ± 0.6 vs 1.7 ± 0.4 / h, $p<0.05$) and mixed reflux episodes (0.5 ± 0.2 vs 4.1 ± 0.5 / h, $p<0.05$) increased significantly after the meal. Postprandially, liquid and mixed reflux events were acidic in 66.7 % and 49.2 % respectively, while gas reflux was never acidic. The frequency of air swallowing correlated to the size of the postprandial intragastric air bubble ($r=0.39$, $p<0.05$) and to the rate of gaseous gastroesophageal reflux episodes ($r=0.40$, $p<0.05$). The number of air swallows and the size of the intragastric air bubble were not correlated with the number of liquid acid and liquid non-acid reflux episodes. Conclusion: These findings support the concept that, in healthy subjects, swallowing of air leads to an increase in size of the intragastric air bubble and to gaseous reflux but does not affect liquid reflux.

Determination of the minimal sampling frequency for intraluminal impedance measurement of the esophagus

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Electrical impedance monitoring is promising as a new tool for measurement of esophageal transit and gastroesophageal reflux. In all systems for impedance monitoring the signals are stored in digital format after analog-to-digital (A/D) conversion at a predefined rate, the sampling frequency. We aimed to find the minimal required sample frequency for esophageal transit and gastroesophageal reflux studies using electrical impedance monitoring. An intraluminal impedance system was used at a sample frequency of 1000 Hz. Ten 5-mL swallows were studied in 10 fasting healthy subjects. Gastroesophageal reflux was monitored in these subjects and in 5 reflux patients during a 90-min postprandial recording period. A specially designed computer program was used to derive, from the original 1000-Hz file, series of new data files with sample frequencies of 500, 200, 100, 50, 20, 10, 8, 5 and 4 Hz. In the analysis of the wet swallows, bolus head advance time (BHAT) and total bolus transit time (TBTT) were measured for all frequencies. Liquid and gas reflux episodes were identified and propagation velocity and maximum amplitude of impedance of gas reflux and liquid reflux events were calculated for all frequencies. The detection of gas and liquid transport remained possible down to a sample frequency of 50 Hz. At lower sample frequencies, propagation of gas became increasingly undetectable (0% at 50 Hz, 9.5% at 20 Hz, 35.7% at 10 Hz, 59.5% at 5 Hz). Errors in BHAT at lower sample frequencies were larger than errors in TBTT, making BHAT the limiting factor. Errors for BHAT increased from 1.6% at 10 Hz to 1.9% at 8 Hz, 3.3% at 5 Hz and 10.7% at 4 Hz. Conclusion: In intraesophageal impedance measurement the minimal sample frequency is 50 Hz for reflux monitoring and 8 Hz for esophageal transit testing. These settings lead to a substantial reduction in data storage space and processing time while still allowing detection of all relevant impedance phenomena.

Increased oesophagogastric junction (OGJ) bolus transit time is related to postfundoplication dysphagia

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Although dysphagia is prominent among symptoms after fundoplication, its relationship with bolus transit across the oesophago-gastric junction (OGJ) is incompletely defined. The aim of the study was to assess bolus transit across the OGJ in relation to OGJ dynamics and symptoms of dysphagia in patients before and after laparoscopic fundoplication.
Ten (7 male, 3 female) patients were studied (mean age 47 (3.4) yrs) before and 3 months after fundoplication. Simultaneous OGJ manometry and videofluoroscopy were performed with patients swallowing 5 liquid (10 mL barium suspension) and 5 solid (1cm^3) bolus consistencies in upright position. Manometry was done with a perfused assembly with side holes in the pharynx, the esophagus, and 11 side holes (1 cm apart) straddling the distal esophagus, the OGJ and the proximal stomach. Symptoms of dyphagia were scored and videofluoroscopic images were analyzed for the total esophageal and OGJ transit time. Manometric tracings were analyzed for the nadir OGJ relaxation pressure, relaxation duration and distal peristaltic amplitude for each bolus.
Fundoplication increased OGJ transit time, from 7.4±1.0 s to 9.8±1.1 s for liquids (*P*=0.018) and from 2.9±0.6 s to 6.1±0.9 s for solids (*P*=0.015), whereas esophageal transit time was not affected by fundoplication. No relationship between OGJ transit time and dysphagia was observed before fundoplication. In contrast, a significant relation was observed for both liquids (r=0.72, *P*<0.01) and solids (r=0,75, *P*<0.05) after operation. Nadir OGJ relaxation pressure increased for both liquids (*P*=0.018) and solids (*P*=0.019) but did not correlate with dysphagia or OGJ transit time. Distal peristaltic amplitudes and duration of OGJ relaxation were both not affected by fundoplication.
Conclusions: 1) Fundoplication increases the OGJ transit time for both liquids and solids. 2) Postfundoplication dysphagia is related to increased transit time across the OGJ for both liquids and solids.

Endoscopic Anti-reflux Therapy: Effect of Radiofrequency Energy Therapy on Reflux Mechanisms and Vagus Nerve Function

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A new endoscopic technique involving the delivery of radiofrequency energy (RFe) to the gastroesophageal junction (Stretta®) has been shown to significantly improve symptoms in patients with gastroesophageal reflux disease (GERD). However, the mechanisms by which RFe exerts its anti-reflux effect are poorly understood. Transient lower esophageal sphincter relaxations (TLESRs) are the major mechanism of reflux in patients with GERD. Our aim was to explore the effect of RFe on reflux mechanisms. Since anti-reflux surgery may jeopardize the vagus nerve, vagus nerve function was also evaluated.
Methods: Twelve patients with reflux symptoms and documented GERD (7F 5M, mean age 48 yrs) were studied. Patients underwent 24-hour pH metry, fasting and postprandial combined manometry/pH metry, prior to RFe and 6 months after. Vagus nerve function was tested by measuring plasma pancreatic polypeptide (PP) secretion in response to insulin-induced hypoglycemia.
Results: RFe reduced ambulatory acid exposure from 9.9±2.7% to 5.8±2.3% ($p=0.3$) at 6 months after RFe. LES pressure increased from 13±1mm Hg to 17±2 mmHg ($p=0.01$). Postprandial TLESR frequency decreased significantly from 3.7±0.7 to 2.4±0.7 ($p<0.01$). Furthermore, also TLESRs associated with acid reflux decreased from 45 to 30%. The number of reflux episodes due to mechanisms unrelated to TLESR (i.e. absent LESP, LESP drift or strain) was not affected by RFe: 2.4±0.3 and 2.4±0.4 per hour respectively. The peak PP response to hypoglycemia decreased after RFe from 187±25 to 117±26 pM ($p<0.05$). In 2 patients the PP response post-RFe was compatible with complete vagus nerve dysfunction (peak plasma PP<47pM).
Conclusions: RFe effectively controls symptoms in patients with GERD. The anti-reflux effect of Rfe is due to a significant reduction in TLESRs. The results of the vagus nerve test indicates that disruption of vagal pathways may occur due to RFe. Further evaluation of vagal nerve function in response to RFe is needed.

The relationship between gastric volumes and dyspeptic symptoms assessed by SPECT scanning after the drink test in healthy volunteers

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Abnormal sensitivity to distension of the distal or proximal stomach has been described in patients with functional dyspepsia (FD). The gold standard to assess gastric sensitivity is the barostat, which is however invasive, not physiologic and usually only assesses one part of the stomach. We previously showed that a water drink test is a good tool to evoke dyspeptic symptoms discriminating healthy volunteers (HV) from patients with FD. To what extent these symptoms are related to distension of the proximal or distal stomach is unclear. Therefore, we determined gastric volumes after a drink test using SPECT scanning. After a baseline scan 20 HV (7 m, 13 f; age 25y (19-52y) underwent a drink test (100 ml/min) followed by 5 scans up to 120 min. Symptoms (bloating, nausea, pain, satiety, fullness, hunger and burning) were scored on a Visual Analogue Scale (0-100) before every scan. The ingested amount of water was 1818 ± 153 ml. The volume increase of total, proximal and distal stomach after the drink test was respectively 2181 ± 149 ml, 1606 ± 115 ml and 574 ± 49 ml. The surface area of the proximal and distal stomach increased after the drink test with 140 ± 9 cm2 and 38 ± 4 cm2 respectively. There was a graduate decrease in volume over time. After 1h 34% and after 2h 14% of the total gastric volume remained. A mixed effects model with random effects for each patient on each factor showed that the variation in symptoms of bloating, satiety, fullness, hunger and nausea are respectively 88%, 89%, 88%, 64% and 79% explained by the volume of the proximal stomach. Distal stomach volume and surface areas were less powerful as the proximal stomach volume in explaining variations in symptoms.
Conclusion: These data suggest that in HV dyspeptic symptoms after a drink test are predominantly associated with proximal stomach volume. Whether the gastric distribution of ingested water and its relationship with symptoms is altered in patients with FD is currently evaluated.

Assessment of visceral sensitivity using radio telemetry in a rat model of maternal separation

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Stress plays an important role in the development of visceral hypersensitivity, a key mechanism underlying the pathophysiology of the irritable bowel syndrome. In animal models used to evaluate stress related visceral hypersensitivity, animals are mostly restrained during the assessment of the visceromotor response (VMR) to colon distension. We developed an animal model using implanted radio telemetry for remote detection and measurement of abdominal EMG in non-restrained animals. Long Evans pups were subjected to a maternal separation protocol. Control animals were not handled. At the minimal age of 12 weeks, a telemetry transmitter and EMG electrodes were implanted in the abdominal cavity and in the abdominal muscles respectively. After a 10 day recovery period visceral sensitivity was evaluated in freely moving rats by colorectal distention using a balloon catheter positioned in the distal colon. The distention protocol (1, 1.5 and 2 ml) was performed before, directly after and 6 and 24 hrs after 1 hour water avoidance (WA). The area under the curve of the EMG recording during distension was determined and normalized to the percentage of the pre-WA maximal response. All animals recovered well from surgery and tolerated the distention protocol while freely moving. In both control and separated animals, distension with increasing volumes resulted in a similar pre WA volume-dependent increase in the EMG signal. After WA, there was no change in the VMR at any of the time points studied compared to baseline in non-separated rats. In contrast, in separated animals, VMR was significantly increased directly after, 6 and 24 hrs after WA stress ($p<0.05$*, Wilcoxon signed rank, n=7). Sham WA did not affect sensitivity. Conclusion Our results show that radio telemetry is a reliable new tool to evaluate visceral sensitivity in small animals. These data further confirm that maternal separation is a good stress model leading to altered response to acute stress.

Rectal compliance is disturbed in children with severe constipation

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Decreased rectal sensation assessed with volume distension, is considered the major abnormality in children with constipation. However, using this technique, the thresholds of sensation are largely dependent on rectal compliance. Therefore, to avoid this methodological pitfall, rectal sensation should be assessed using pressure controlled distension. So, thresholds for rectal sensation (first sensation, urge to defecate and pain), and compliance were determined using a pressure controlled, distension protocol. 69 patients with severe pediatric constipation (PC) (50 M, mean age 10.9 ± 2.2 years) were studied and compared with 22 healthy volunteers (HV) (11 M, mean age 12.7 ± 2.6 years).
Mean (±SD) sensation thresholds were not different between the 2 groups. A subgroup of only 12 patients (17%) showed decreased rectal sensation for urge (cutoff: mean of HV + 2SD) (ns). Rectal compliance in PC was significantly higher (24 ± 9 ml/mmHg) compared to HV (16 ± 2 ml/mmHg) ($p<0.0001$). In 58% of the PC patients we found an abnormal rectal compliance (cutoff: mean of HV + 2SD), whereas the rectal compliance was within the normal range in all HV ($p<0.0001$). Of all patients with an abnormal urge during barostat, 75% (9/12) had an abnormal compliance (ns). 22.5% (9/40) of PC patients with an abnormal compliance, also had an abnormal sensation for urge ($P<0.001$). Abnormal compliance was associated in 60% (24/40) of patients with a scybalus at intake. Normal rectal function (sensation, compliance) was found in 38% of the PC patients.
Conclusions: Increased rectal compliance is the most prominent feature in children with severe constipation. Surprisingly, sensation for urge is only disturbed in 17% of these children. The increased rectal compliance explains the high percentage of abnormal rectal sensation reported earlier in studies, using volume controlled distension. Rectal fecal impaction at intake is not predictive for an abnormal rectal compliance.

A scoring method on plain abdominal x-rays in the diagnosis of childhood constipation revisited

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A plain abdominal x-ray is frequently used to confirm faecal retention in children with constipation. Recently a new scoring system (Leech et al 1999) has been published to evaluate the severity of constipation on an abdominal x-ray. In the present study our aim was to assess the value of the Leech-scoring method in children with functional defecation disorders and compare this method to the Colonic Transit Time (CTT) measurement (Bouchoucha et al. 1992). 89 consecutive children (58% boys, median age 9.8 yrs) with functional gastrointestinal disorders were included in the study. Based on clinical parameters, 51 fulfilled the criteria for constipation, 7 and 31 children fulfilled the criteria for functional abdominal pain (FAP) and functional non-retentive fecal soiling (i.e. non constipated group), respectively. Three observers independently assessed both the CTT-measurement and the Leech-score on each x-ray. After 4 weeks the same observers evaluated the same x-rays in a similar fashion. A significant difference was found between constipated patients and non-constipated children in both the CTT and mean Leech-scores (95 vs.36 hours and 10.4 vs. 8.5 points, respectively). The sensitivity and specificity of the CTT measurement were 71% and 97%, respectively. The sensitivity and specificity of the Leech-scoring method, were 73% (range 46-80%) and 58% (29-79%), respectively. Disappointingly however, the Leech scoring method showed a significant intra-and inter-observer reliability ($p<0.001$ and $p<0.001$).
Conclusions: The Leech-scoring method on a plain abdominal x-ray in the diagnosis of children with functional defecation disorders is of limited value. Besides a low sensitivity and specificity a high intra– and inter observer variability was found. The CTT method showed a similar sensitivity but a very high specificity in children with defecation problems.

Diurnal Pattern and Reproducibility of Colonic Motility during Ambulatory Recording

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Recently, prolonged ambulatory manometry of the colon has become technically feasible. With the technique relevant data concerning colonic (patho-)physiology can be obtained. Of the colonic motor events especially High-Amplitude Propagated Contractions (HAPC's) have a role in colonic transport. Little is known, however, on HAPC's, especially on their diurnal pattern, meal-response and reproducibility.
Our aim was to investigate 1) diurnal variation in colonic motility, more specifically in HAPC's and 2) reproducibility of prolonged ambulatory colonic manometry.
Nine healthy volunteers (7F, age 39±3 yrs) underwent 24-hr colonic manometry on two consecutive days. A solid-state pressure catheter with 6 sensors (n=2 hepatic flexure, n=2 splenic flexure, n=2 sigmoid) was endoscopically positioned in the colon. Subjects were ambulatory with standardized resting and eating conditions. Colonic motility was evaluated by calculation of a motility index (MI = wave frequency*mean amplitude*mean duration; 10^3 sec*mmHg) per hour and by counting HAPC's (≥3 sensors; ≥80 mmHg).
HAPC-counts were 4.8±1.0 (day 1) and 5.4±1.1 (day 2), with a correlation coefficient of R=0.6 (P<0.001). Upon going to sleep, HAPC-frequency decreased from 0.33±0.11 to 0±0 per hour (P<0.05). Upon waking, HAPC-frequency increased from 0.06±0.03 to 0.5±0.15 per hour (P<0.05). After meal-ingestion HAPC-frequency increased from 0.11±0.04 to 0.29±0.09 per hour (P<0.05).
Colonic MI decreased from 13.0±2.2 to 8.5±1.6 per hour upon going to sleep (P<0.05) and increased from 7.2±0.8 to 16.2±2.2 per hour upon waking (P<0.05). The increase of colonic MI upon eating was not significant. Colonic MI had a correlation coefficient of R=0.3 (P<0.001) between day 1 and day 2.
Conclusions: Under standardized conditions colonic motor activity and HAPC's are reproducible in healthy volunteers. HAPC's and colonic motility show a diurnal pattern. A postprandial response was observed only for HAPC's, not for colonic motility.

Tumor necrosis factor-alpha and interleukin 10 gene polymorphisms in Irritable Bowel Syndrome

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Some patients develop Irritable Bowel Syndrome (IBS) after acute gastroenteritis. Imbalances in the genetically controlled pro- and anti-inflammatory cytokine production may promote ongoing low-grade inflammation and subsequent IBS symptoms (post-infectious IBS, PI-IBS). Therefore, we studied gene promoter single nucleotide polymorphisms (SNP) of interleukin 10 (IL-10, anti-inflammatory) and tumor necrosis factor alpha (TNF-α, pro-inflammatory) that may be associated with disease expression. DNA was extracted from peripheral blood leucocytes of 111 IBS-patients (age 48 ± 1 yr, Rome II), 23 of whom had a history of acute gastroenteritis, and 162 healthy controls (age 37 ± 1 yr). We analyzed SNP at positions G–1082A and C–819T of the IL-10 gene and at G–308A of the TNF-α gene to assess genotype frequencies. IBS-patients had significantly higher frequencies of the intermediate producer TNF-α genotype (one high producer allele, -308*A) compared to controls (41% vs 26%) (p=0.02). Homozygous high producers were rare (2.6% overall). High, intermediate and low producers of IL-10 made up 26%, 51% and 23% vs. 28%, 51% and 21% in the case of the –1082 SNP (patients vs. controls, p=0.93) and 6%, 36% and 58% vs. 8%, 38% and 54% for the –819 SNP (patients vs. controls, p=0.85). None of the genotypes was associated with PI-IBS. The intermediate producer genotype for TNF-α was more prevalent in PI-IBS patients (G/A; 48%) compared to other IBS-patients (39%) and controls (26%) (p=0.07), and in diarrhea-predominant IBS (54%) compared to constipation (37%) and alternating subtypes (27%) (p=0.06).
Conclusion: The heterozygous TNF-α G/A genotype is more common in IBS-patients, but IL-10 –1082 and –819 SNP genotypes are similarly distributed between patients and controls. PI-IBS is associated with a higher frequency of the TNF-α intermediate producer genotype. Different IBS-subgroups have diverse cytokine genotypes that might contribute to the specific disease phenotype.

Gastric acid-suppressive drugs and the risk of community-acquired pneumonia.

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Reduction of gastric acid secretion due to acid suppressive therapy allows pathogen colonization from the upper gastrointestinal tract. The bacteria and viruses in the contaminated stomach have been identified as species from the oral cavity.
We studied the association between the use of acid suppressive drugs and community-acquired pneumonia in a population based cohort study.
The risk of community-acquired pneumonia was estimated in relation to prescribed gastric acid suppressive drugs (H2 receptor antagonists and proton pump inhibitors) as documented in the Integrated Primary Care Information database. Rates and crude relative risk were calculated based on the incidence of pneumonia in non-exposed and exposed subjects. To reduce confounding by indication a nested case control analysis was conducted to compare the effects of the different acid-suppressive drugs among persons who had ever used acid suppressants during the study period.
The study population comprised 364683 subjects with a total of 5551 pneumonias. The incidence rate of developing pneumonia in non acid suppressive drug users and acid suppressive drug users was 0.55 and 2.45 per 100 person-years, respectively. The adjusted risk for pneumonia among persons who never used H2 receptor antagonists and were currently exposed to proton pump inhibitors was 1.89 (95% confidence interval: 1.36-2.62) compared with past proton pump inhibitor users. Among persons currently exposed to H2 receptor antagonists and never to proton pump inhibitors the adjusted risk ratio was 1.63 (95% confidence interval: 1.07-2.48).
In conclusion, persons using gastric acid suppressive therapy have an increased risk of community-acquired pneumonia.

Influence of pretreatment with a proton pump inhibitor (PPI) on Helicobacter pylori eradication: a meta-analysis

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There is much debate about the influence of pretreatment with a PPI on H. pylori eradication. Pretreatment used to be advocated, even though it was found to be associated with therapy failure for dual therapy. The few studies investigating the influence of pre-treatment on triple and quadruple therapies did not find differences in eradication rates. However, the high eradication rates of triple/quadruple therapies make it difficult to study factors associated with therapy failure in small populations. In order to overcome this problem we performed a meta-analysis.
The Cochrane Controlled Trials register, MEDLINE, Current Contents and Cinahl, (to June 2003) as well as abstracts from major gastroenterological meetings (1994-2003) were searched. Only randomized clinical trials comparing a regimen for H. pylori eradication without pretreatment with a PPI with exactly the same regimen with pretreatment were included. The overall risk difference (with - without pretreatment) was calculated by pooling the risk differences of the individual studies weighted by the inverse of the variance.
Nine studies, investigating 773 patients, were identified. There was considerable variation regarding therapy regimen (2 studies used quadruple therapy, 6 used different triple regimens and one used omeprazole/-amoxicillin/metronidazole/roxithromycin), therapy duration (2-14 days) and pretreatment duration (3-49 days). Study size ranged from 36-116 patients. The overall risk difference was 0.1% (95%CI: -5%;5%). The pooled risk-difference was -6.3% (-18%;6%) for quadruple therapies (n=192) and 2.7% (-3%;9%) for triple therapies (n=491). The number of studies was too small to detect sources of heterogeneity.
Conclusions: Pretreatment with a PPI does not seem to influence H. pylori eradication. An adequately sized trial (n=500) using standard therapy is needed to definitely settle the issue.

Esophageal function after correction of esophageal atresia: follow-up after more than eighteen years

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Primary repair of esophageal atresia (EA) restores gastrointestinal continuity, but does not ensure a normal esophageal function. The aim of this study was to evaluate esophageal function in adults after correction of EA.
We included 25/57 patients (44%) treated for EA, age 18-42 years. They underwent esophageal manometry and ambulatory 24-hour pH measurement. Manometry was performed using a catheter with 3 pressure transducers at 5 cm distance. The pH probe was positioned 5 and 20 cm above the manometrically established upper border of the lower esophageal sphincter (LES), position was checked by X-ray. The pH values (sample time 5 seconds) were calculated using the criteria of Johnson and Demeester.
Esophageal manometry was performed in 20 patients, since introduction of the catheter was impossible in 5 patients due to esophageal stricture. The mean LES pressure was 13 mm Hg (range 5-35); sphincter relaxation was complete in all patients. Esophageal body motility (determined with 6 wet swallows of 5 ml water) was non-specifically disturbed in 19/20 patients (95%). The mean percentage of propulsive swallows was 24% (range 0-87%); mean percentage of non-transmitted swallows was 44% (range 17-100%). The amplitude of esophageal body contractions was normal in 6 patients (30%), moderate in 10 (50%), and low in 4 (20%). pH measurement showed a normal pattern in 16 patients (80%), minor reflux in 1 (5%), and pathological reflux in 3 (15%). Two of the patients with pathological reflux had used anti-reflux medication in the past, but did not have complaints at the time of the study.
Conclusion: This study shows a high percentage of esophageal motility problems and a moderate percentage of gastro-esophageal reflux after correction of EA. Further studies will be undertaken to investigate the correlation between these results, quality of life measurements and findings at esophagogastroscopy.

Relationship between Upper Gastrointestinal Symptoms and Partial Gastric Volumes Measured by 3-Dimensional Ultrasonography

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Accommodation of the stomach and postprandial volume distribution are key factors in the generation of upper abdominal symptoms. The aim of this study is to investigate the effect of proximal and distal gastric volume distribution on upper abdominal symptoms in healthy volunteers (HV), patients with functional dyspepsia (FD) and GERD patients in response to a liquid nutrient. 35 HV (16 male, age 30.4±10, range 18-53), 20 FD patients (7 male, age 44.7±12, range 21-69) and 20 GERD patients (12 male, age 48.9±11, range 29-69) participated. Ultrasonographic data were acquired while fasting and at 5, 15, 30, 45 and 60 min after meal ingestion (200 ml nutridrink + 300 ml water, 300 kCal) within 3 minutes. Sensations (epigastric pain, fullness, nausea and hunger) were scored using a VAS. The increase in total gastric volume 5 minutes postprandially in FD (455.1±33.9 ml) and GERD patients (481.8±47.6 ml) was comparable to HV (463.6±34.0 ml, p = NS). The increase in distal volume in FD and GERD patients was significantly higher compared to HV ($p<0.0001$, $p=0.008$ resp). The increase in proximal volume was less in FD patients ($p<0.0001$) compared to HV. In contrast, the proximal volume was higher in GERD patients ($p<0.0001$) compared to HV. For all participants (n=75), the increase in distal volume was related to fullness (5 min $r = 0.584$, $p<0.0001$; 15 min $r = 0.522$, $p<0.0001$). Moreover a negative correlation was observed between the increase of proximal volumes and fullness (5 min $r = -0.329$, $p=0.004$; 15 min $r = -0.379$, $p=0.001$). No relation was found between proximal or distal volumes and hunger, nausea or upper abdominal pain. The sensation fullness is associated with an increase in distal gastric volume in all participants. Accommodation of the proximal stomach in FD patients is impaired which may contribute to the augmented distal stomach volumes and greater fullness sensations.

Colorectal motor and sensory function in constipated and non-constipated patients after hysterectomy

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We have recently shown that 22% of post-hysterectomy (PH) patients develop constipation after the operation, but the mechanism is not known. Hysterectomy interferes with pelvic anatomy and may cause pelvic nerve injury. Our aim was to study rectal and colonic motor and sensory function in PH patients with and without newly developed constipation. We evaluated rectal and colonic compliance (ramp distensions 5-30 mmHg) and urge and pain perception (VAS 0-10 cm) in 10 PH patients with constipation (age 45 $\pm$ 1.5 yrs; $\leq$ 2 bowel movements per week or evacuation disorder), 10 without new onset constipation (age 51 $\pm$ 2.8 yrs) and 25 healthy female volunteers (age 38 $\pm$ 2.7 yrs) using a computerized barostat assembly (balloons in rectum and descending colon). PH-patients as a group had significantly lower rectal compliance compared to controls (8.5 $\pm$ 0.9 vs 10.5 $\pm$ 0.5 ml/mmHg respectively, p=0.045), but compliance did not differ between patients with and without constipation. Sensation of urge at 30 mmHg rectal pressure was impaired in both constipated patients (1.1 $\pm$ 0.5 cm) and non-constipated patients (2.4 $\pm$ 0.9 cm) compared to controls (5.6 $\pm$ 0.5 cm, p=0.002). Pain did not increase significantly during rectal distensions, neither in patients nor in controls. Colonic compliance was not significantly different between constipated (8.8 $\pm$ 0.9 ml/mmHg) and non-constipated (6.3 $\pm$ 1.0 ml/mmHg) patients and controls (7.6 $\pm$ 0.4 ml/mmHg). Urge and pain perception during colonic distensions were not significantly increased compared to basal and not different between patients and controls.
Conclusion: Rectal, but not colonic, motor and sensory function is impaired in patients after hysterectomy. No differences in rectal function were observed between constipated and non-constipated PH patients. These findings point to local injury after the hysterectomy procedure.

Rectal function in functional non-retentive fecal soiling (fnrfs)

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To date children with FNRFS are believed to suffer from a mental disturbance. To what extent abnormalities in rectal function may be involved, has not been evaluated.
We evaluated rectal sensation and compliance in these patients using the barostat. Rectal sensation (first sensation, urge to defecate and pain), and compliance were determined using a barostat (pressure controlled, intermittent distension procedure).
Rectal function was evaluated in 19 children with FNRFS (15 M, mean age 10.0 ± 1.9 yrs) and compared with 22 healthy volunteers (11 M, mean age 12.7 ± 2.6 yrs) (HV).
Mean sensation thresholds (first sensation, urge to defecate and pain) were not significantly different from HV. Moreover, mean rectal compliance in FNRFS (14 ± 4.0 ml/mmHg) was not significantly different from HV (16 ± 2 ml/mmHg). A subgroup (4/19) of FNRFS patients showed an abnormal rectal function: 2 patients (11%) showed disturbed rectal sensation for urge (cutoff: mean of HV + 2SD). Additionally, another 2 patients (11%) had an abnormal rectal compliance (cutoff: mean of HV + 2SD).
Conclusions: Rectal function is normal in the majority of patients with FNRFS underscoring that fecal retention does not play a role in the symptomatology in this patient group. However, in a subgroup, increased compliance (11%) or decreased sensation (11%) can be demonstrated suggesting impaired rectal function as possible underlying pathophysiological mechanism.

Follow-up of children with unrecognised coeliac disease (CD) identified after mass screening.

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Aim. Assessment of health effects after mass screening on CD. Methods. Prospectively, 4 years assessment of 32 CD children identified by mass screening in 1998 and treated with either a gluten-free (GFD) or a normal diet (ND). Our intention was to allocate the children for treatment by stratified randomisation. The Ethical Committee approved the study. Results. The parents of 18 children did not accept randomisation: 11 children with symptoms and 1 without were treated, while 6 symptom-free children were not. The rest were randomised to a GFD (7) or to a ND (7). One year after screening small bowel biopsies showed mucosal recovery in all the treated children and in 1 eating gluten. Symptomatic children had a decreased health related quality of life (QoL) that improved significantly after GFD. Four years after screening the health status was significantly improved in all the treated children. 7 Out of the 12 symptom-free children with ND developed symptoms and 6 of them were successfully treated. 2 Symptom-free children stopped the GFD: 1 re-started it because of symptoms after ND. 24 Children (77%) followed a GFD.
Conclusions: Treatment improved the health status and QoL of 41% children and it may have prevented significant morbidity in another 22%. CD is a candidate for secondary disease prevention by mass screening.

Gene expression and mapping of nutrient regulated biological pathways in the human small intestine

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Many genes are expressed in the human small intestine. No data are available about genome-wide gene expression profiles in the human small intestine, or about the ability to regulate gene expression by nutritional interventions.
Five volunteers (22+/-2 y) were tested on two occasions. Duodenal biopsies were obtained by gastroduodenoscopy. Subsequently, a perfusion catheter was inserted into the proximal small intestine with an injection port located in the proximal descending duodenum, which enabled continuous perfusion of a 40-cm segment of the proximal small intestine with either 80 or 400 mg iron as ferrous gluconate for 30 min. Subsequently, a second gastroduodenoscopy was performed. Tissue samples from 2 and 3 volunteers respectively, were pooled for microarray analyses. Gene expression profiles in the pooled tissue samples were measured using genome-wide microarray chips. Information about biological processes affected by the iron challenges were investigated using GenMAPP software (http://www.GenMAPP.org).
Among 8542 genes expressed in the baseline tissue samples, 28 genes were statistically increased, whereas 61 genes were significantly downregulated after administration of the low- and high iron dose. GenMAPP analysis revealed that both iron challenges strongly mediated a number of processes, which were associated with G-protein receptor-associated signal transduction, cell cycle, calcium channels and complement activation. Most results differed between the two pools and between the two different iron dosages, although it was not possible to investigate this satistically.
Conclusion The microarray technology profiles provides a useful tool to generate research hypotheses to design further studies to largely unknown phenomena, such as the response of intestinal mucosa on nutrient interventions. Individual tissue samples should not be pooled in order to reduce costs of analyses, as this will cause loss of important information.

Ghrelin and leptin levels in restrictive surgery, a 2 year follow-up study

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Ghrelin is a recently discovered gastric hormone, which has an orexigenic effect. Administering ghrelin to rodents leads to an increase in food intake. Morbid obese individuals have lower ghrelin levels compared to lean persons. After gastric bypass these levels remain low, whereas in restrictive surgery the behavior of ghrelin postoperatively is not known. It is hypothesized that the difference in success percentage of gastric bypass and restrictive bariatric interventions is due to a different behavior of ghrelin after bariatric surgery. In order to elucidate this hypothesis we studied the behavior of two satiety hormones, ghrelin and leptin, pre-, 1 and 2 years postoperatively after restrictive surgery.
In a prospective study, 18 morbid obese patients received restrictive surgery (Lapband or VBG). Plasma ghrelin and leptin levels were evaluated preoperatively, 1 year and 2 years postoperatively.
During these 2 years BMI decreased from 51 $\pm$ 5 to 32 $\pm$ 3 kg/m^2. Fasting plasma leptin levels were significantly lower after 1 and 2 years of surgery ($p<0.001$). Plasma ghrelin levels rise 1 year ($p<0.05$) and 2 years ($p<0.02$) postoperatively.
After bariatric surgery the morbid obese individual receives orexigenic signals due to the falling leptin levels. The additional rise in ghrelin levels after restrictive surgery can be the key in understanding the difference seen in success percentage between gastric bypass and restrictive surgery in favor of gastric bypass. These results point out that suppression of ghrelin levels postoperatively could enhance the results of restrictive surgery.
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Endoscopic Resection combined with Photodynamic Therapy for High Grade Dysplasia and Early Cancer in Barrett's Esophagus

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Aim was to prospectively evaluate Endoscopic Resection (ER) combined with Photodynamic Therapy (PDT) for treatment of selected patients with High Grade Dysplasia and Early Cancer (EC) in Barrett's Esophagus (BE). Patients with either type I/II lesions <2cm or lesions >2cm and major contraindications for surgery and no signs of submucosal infiltration at EUS, standard and fluorescence endoscopy, underwent a diagnostic ER, using a flexible large calibre ER-cap. Patients with T1sm tumors in their ER-specimen were referred for surgery. Patients with T1m or less received additional endoscopic therapy (ER a/o PDT) in case of HGD/EC in lateral resection margins or when piece-meal resection impaired judgement of lateral margins. 5-ALA (40mg/kg) was used for PDT (100J/cm^2). Patients were followed up every 3 months the first year, every 6 months the second year and yearly thereafter.
Between Jan '01 and Dec '02, 33 patients underwent a diagnostic ER. There were no significant complications. Endoscopic treatment was discontinued in 5 patients (T1sm tumors: n=4, patient's preference: n=1). Of the remaining 28 patients, 5 were considered sufficiently treated with the initial ER and entered follow up (FU). 23 patients received additional endoscopic treatment, complicated in 3/23 patients (2 mild post-PDT hypotension, 1 moderate stenosis which resolved after dilatation). In 2/28 patients, endoscopic treatment failed (persisting HGD: n=1, poor healing EMR-ulcer: n=1) and these patients were referred for surgery. During a median FU of 15.2 months, 5/26 patients showed recurrence of HGD in their biopsies. All were successfully re-treated with ER. At the end of FU, 26 of 28 patients are in local remission: success-rate 93%.
ER with additional PDT is a safe and effective alternative for surgery for selected patients with HGD/EC in BE. Tissue diagnosis with ER is imperative for optimal patient selection. Local recurrences do occur, but can successfully be retreated endoscopically.

Endoscopic Treatment of Barrett's neoplasia

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Introduction Barrett's esophagus is associated with a 50-100x increased risk of developing adenocarcinoma. Cancer development is preceded by dysplastic changes. Until recently, radical surgical resection was considered standard therapy for high-grade dysplasia (HGD) and early invasive carcinoma. Surgical therapy, however, caries a mortality rate of 3-10 % and long-term morbidity in the range of 45-75 %. Advances in endoscopic intervention techniques make these malignancies amenable for local therapy. We present our results using multi-modality endoscopic ablation.
Patients and Methods: From 2001 to 2003 subsequent patients with HGD and T1m invasive carcinoma were considered for endoscopic treatment. Endoscopic mucosal resection (EMR) was performed for staging if the neoplasia could be localized. Photodynamic therapy (PDT) was performed at 633 nm using the oral photosensitizer 5-Aminolevulinc Acid at a dose of 40mg/kg. Follow-up endoscopy with biopsies was performed at 3 months and subsequently every 6 months.
Results: Twenty-two patients (6 female, 16 male; mean age 66 years, range 46-82) were treated according to the protocol. Capped EMR was performed in 18/22 patients. PDT was performed 6 weeks after EMR. No major complications occurred. At 3 months 18/22 (82%) patients were in remission: 11/11 HGD and 7/11 T1m carcinomas. At an average follow-up of 10.6 months (3-25), one metachronous HGD was detected. Of 4 treatment failures, 2 underwent curative esophagectomy, 1 was considered unfit for surgery, and 1 refused surgery.
Conclusions: Endoscopic ablation of high-grade dysplasia and early invasive cancer is safe and effective. After careful staging, local therapy in an experienced center should be considered as an alternative for surgical esophagectomy.

Endosonographic staging of obstructive esophageal cancer: how far should we go?

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Endoscopic ultrasonography (EUS) is a valuable tool in staging esophageal cancer. TNM-staging accuracy decreases in stenotic esophageal cancer when visualization of the tumor is incomplete. Little is known about the best strategy in pre-treatment staging in stenotic esophageal cancer. In the USA patients are often carefully dilated to facilitate passage of a standard EUS instrument. In Europe patients are either staged using a slim ultrasonic probe, a miniprobe, or surgery is performed without complete endosonographic evaluation. To determine the optimal strategy we studied the outcome of patients with non-traversable esophageal cancer.
Esophageal staging EUS examinations between 1999 and 2003 with a minimal follow-up of 6 months were analysed. Data were collected regarding location of stenosis, histology, operative results and outcome. The Olympus GF-UM20 radial echoendoscope (diameter 13.2 mm) was used.
718 patients were analysed (70% adeno; 30% squamous). In 157 patients (22%) the tumour could not be passed (65 % adeno; 35% squamous; p=0.29). EUS staging in these patients was incomplete. Of these 157, 56 underwent primary surgery. Of these 56 patients, 23 (41%) were irresectable due to local invasion (T4) or metastatic disease; 8 had liver or peritoneal metastases (M1b disease); 15 had T4 and/or M1a disease and could therefore have been detected by standard EUS with dilation or slim ultrasonic probe (65%), or by miniprobe EUS (43%). Of the remaining 33 patients, 24 underwent a microscopically radical resection (R0), 9 were microscopically irradical (R1). Disease-free survival after R0 resection was 46% and after R1 resection 27%. Overall 6 months disease-free survival was 27% (15/56).
Conclusions: The prognosis in severely stenotic esophageal cancer is poor. Maximal effort should be put in complete endosonographic staging since potentially 65% of primarily irresectable tumours could have been detected by EUS and surgery could have been avoided.

Endoscopic screening for synchronous esophageal cancer in patients with head and neck cancer

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Background: Patients with a primary head and neck cancer have an elevated risk for squamous cell carcinoma of the esophagus, due to a high exposure to nicotine and ethanol. Several studies suggest a clinically significant rate of esophageal neoplasms can be detected by routine esophagoscopy. Vital staining of the esophageal mucosa with iodine containing Lugol dye can detect dysplastic squamous epithelium, enabling more directed biopsy.
Aim: Evaluation of the diagnostic yield of routine esophagoscopy supplemented with vital staining with 3% Lugol dye contributes to a more effective detection of squamous cell esophageal cancer at an early stage in patients with smoking and ethanol related head and neck cancer.
Patients and methods: During 2000-2002 a prospective study was performed in 102 head and neck cancer. They underwent routine upper GI endoscopy with a videoendoscope aimed at the detecting of minor esophageal abnormalities. At withdrawal the esophageal mucosa was sprayed with 20-30 ml 3% Lugol dye and renewed esophageal inspection was carried out. Random biopsies were taken at 30 cm of the incisors and from unstained areas.
The underlying malignancies were located in the oral cavity (n=25), oropharynx (n=40), hypopharynx (n=11) or larynx (n=26).
Results: 14 patients had unstained areas of the esophagus after Lugol application. Biopsy in one patient showed severe dysplasia. In only one patient with a T3N0 oropharynx carcinoma an advanced esophageal cancer with two concurrent early cancers was found. All three areas were unstained with Lugol. However, this patient had dysphagia. In one other patient an advanced asymptomatic gastric cancer was found.
Conclusion: In contrast to several previously published studies, the diagnostic yield of routine esophagosocpy supplemented with vital staining with 3% Lugol for the detection of synchronous esophageal cancer is low in patients with head and neck cancer and should not be performed outside clinical studies.

The trucut biopsy needle in EUS: does it improve the diagnostic yield? Preliminary results of EUS-guided histological tissue sampling in 11 patients.

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Endoscopic ultrasound (EUS) enables detailed visualization of paraluminal organs and structures. By means of EUS-guided fine needle aspiration (FNA) a cytologic specimen of lesions can be obtained. Recently, an EUS-guided trucut biopsy needle (TCB) was introduced (Quick-Core biopsy needle,Wilson-Cook,USA), making it possible to obtain histologic samples. In order to assess the feasibility and safety of TCB, and to determine the additional diagnostic yield of TCB over FNA, we studied 11 patients with mediastinal lymphadenopathy (5), mediastinal mass (2), submucosal mass in the distal oesophagus (2) , retroperitoneal mass near the duodenum (1), and a perigastric mass (1). In all, FNA was performed, using 3 needle passages for each lesion. FNA established a definite diagnosis in 2 patients, (submucosal oesophageal mass and a mediastinal mass: both non small cell carcinomas). FNA was suggestive but not conclusive in another 3 patients: mediastinal mass (thymoma), perigastric mass (stromal tumor), and subcarinal node (adenocarcinoma). FNA was nondiagnostic in 6 patients: mediastinal lymphadenopathy (4), retroperitoneal mass (1) and submucosal oesophageal mass (1). TCB failed for technical reasons in one patient (mass near duodenum). In the remaining 10, two or three histological specimen were obtained. TCB confirmed all diagnostic FNA. TCB established a definite diagnosis in all three patients with suggestive FNA: the diagnosis of thymoma could be confirmed, the stromal tumor could be determined as GIST and the adenocarcinoma could be identified as a metastasis of a mesothelioma. TCB established a definite diagnosis in one patient wit a nondiagnostic FNA: submucosal oesophageal mass (leiomyoma). 5 TCBs were nondiagnostic (mediastinal lymphadenopathy). No complications were seen.
Conclusion: TCB appears to be feasible and safe. It will likely serve as an adjuvant technique after an inconclusive FNA. EUS-TCB may be the first choice for large, readily accessible lesions.

What is the appropriate screening protocol in HNPCC?

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Introduction: Hereditary non-polyposis colorectal cancer (HNPCC) is a dominant inherited syndrome, with a lifetime risk up to 80% of developing colorectal cancer (CRC). The surveillance protocol recommended for mutation carriers and (untested) first-degree relatives consists of bi-annual colonoscopy starting from age 20-25 yrs. There is no consensus whether also second-degree relatives should be included in the program. Another question is whether patients aged between 40 and 60 yrs should be screened more frequently (annually) and whether patients that underwent a polypectomy should undergo re-examination after a year. The aim of the study was to answer these questions.
Methods: We selected all subjects with a known mutation from the Dutch HNPCC registry. All colonoscopy and pathology reports were evaluated. Only those patients with adenomas/carcinomas confirmed by a pathologic report were included in the study.
Results: 617 mutation carriers were identified. In 280 parent-child couples with available medical records at least one confirmed HNPCC-related carcinoma was diagnosed. In 23 couples (8.2%) the child was diagnosed with a carcinoma earlier than the parent.
206 patients aged between 40-60 years were under surveillance. In 13 of these patients a carcinoma was diagnosed within 2 years after colonoscopy, and 5 within one year. All carcinomas but one were at a local stage. A total of 330 mutation carriers had undergone > 2 screening colonoscopies. In 133 colonoscopies at least 1 adenoma was diagnosed. During follow up colonoscopy performed within 1 year only 3 carcinomas were diagnosed and no additional cancer within two years.
Discussion: The current surveillance protocol, i.e. colonoscopy every two years, in first degree relatives independent of age and endoscopic findings appears to be appropriate.

Value of serology in the diagnosis of advanced gastric body atrophy: a study in a Dutch primary community

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Advanced gastric atrophy predisposes to gastric cancer and vitamin B12 deficiency. Little is known about the value of serological screening for advanced gastric atrophy in a primary community. Aim: To study the value of serology in the diagnosis of histological advanced gastric body atrophy (GBA) in the general population. Subjects and Methods: A total of 997 consecutive adult subjects was serologically screened for GBA in a community-based family practice in the Netherlands. 34 subjects (3.4%), (15 M, 19 F; 28-91 yr), were diagnosed as having serological GBA. The serological diagnosis was made by the findings of both hypergastrinema (100 ng/L) and hypopepsinogenemia A (< 17 mg/L) and a low pepsinogen A/C ratio (< 1.6). 24 persons of the group of 34, fulfilling the serological criteria for GBA agreed in undergoing upper gastrointestinal endoscopy and serological retesting. Biopsy specimens from the antrum and corpus were assessed histologically according to the updated Sydney system by 2 expert pathologists. Anti-H.pylori and anti-parietal cell antibodies of the 24 subjects were tested and questionnaires with questions covering stomach diseases and complaints were analysed. Results: At serological retesting 19 of 24 subjects fulfilled the criteria for GBA. Histological examination of the gastric biopsies showed evident GBA in 18 of 24 (75%) and 17 of 19 (89%) subjects with repeat positive serology. One subject with normal serum gastrin at retesting had antral atrophy in addition to GBA. One patient with serological atrophy without histologically documented GBA had severe H. pylori-gastritis preventing optimal estimation of the glandular state. Antral biopsies showed atrophic changes in 6 of the 19 subjects. No adenomatous polyps, tumours or dysplastic alterations were found. Eleven of the 18 persons with GBA identified by histological biopsies had ECL-cell hyperplasia, while H. pylori was identified in the biopsies of 6 of 18 subjects with GBA. H. pylori serology was positive in 11 of 18 subjects, 10 of them had antibodies to parietal cells and 8 of 18 had low serum vitamin B12 levels. No relation was found between atrophy and gastric complaints. Conclusion: Advanced gastric body atrophy was histoogically confirmed in 75% and 89%, after retesting, of subjects selected from a homogeneous autochtonous Dutch primary community by serology. Thus, serology is useful in selecting subjects for endoscopy for advanced gastric atrophy in a primary West-European community. A history of gastric complaints does not aid in selecting subjects for endoscopy.

Barrett's Esophagus after Pneumo-dilation for Achalasia

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Achalasia is characterized by esophageal aperistalsis and defective relaxation of the lower esophageal sphincter (LES). This contrasts with an insufficient LES, which predisposes to gastro-esophageal reflux disease (GERD) and Barrett's esophagus (BE). Because of this paradox, the co-incidence of achalasia and Barrett's esophagus in the same patient is considered to be rare. This is supported by the description of only 30 cases in the literature so far, with only one case of BE after pneumo-dilation.

We hypothesized that effective dilation treatment for achalasia may be associated with the development of BE and studied the incidence of BE in achalasia patients following dilation treatment.

This is a single-center cohort study of 331 patients (160 male; mean age 51 yrs, mean follow up 8,3 yrs) with achalasia who presented at the Erasmus Medical Center from 1975 to 2003. All patients were treated with pneumatic dilation and strictly followed up.

One patient presented with BE at baseline and three patients developed BE after the initial diagnosis but before -delayed- therapy. Twenty-four (7.3%) patients developed BE during follow-up after treatment. Hiatal herniation (HH) was present in 75 (23%) patients. Twenty-one (28%) of them developed BE compared to 7 (3%) of 256 patients without HH (RR 13.8, 95% CI 5.6 to 34.2). Post-treatment LES pressures were slightly lower in patients developing BE than in those without BE (13.9 vs 17.4 mm Hg).

Achalasia patients who are succesfully treated with balloon dilation are at risk for subsequent development of BE. This risk is related to reduced lower esophageal sphincter pressures and the presence of hiatal herniation. These findings support the concept of BE as a complication of gastro-esophageal reflux disease, and have the consequence that succesfully treated patients with achalasia should be considered for surveillance of development of BE, in particular when they have low LES pressures and hiatal herniation

Esophagitis is very common in patients with achalasia after treatment with pneumatic dilatation

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Introduction: Achalasia, an esophageal motor disorder is characterized by aperistalsis and failed relaxation of the lower esophageal sphincter (LES). Treatment aims at lowering of LES pressure. This may enhance the risk of gastro-esophageal reflux disease (GERD), but the incidence of GERD after achalasia treatment is unknown. We studied the incidence and degree of esophagitis and intestinal metaplasia in patients treated for achalasia.
Methods: 378 patients with achalasia were followed with repeated endoscopies and distal esophageal biopsy sampling every 3 years. All patients were initially treated with pneumatic dilatation (PD). Recurrences were treated either with PD (n = 84) or myotomy (MT) (n = 16) depending on initial response. One G-I pathologist blinded to clinical data evaluated all samples. Esophagitis was assessed according to established Ismail-Beigi criteria:(1) basal layer hyperplasia (2) elongation of papillae, (3) dilatation of papillary vascular spaces, (4) intraepithelial inflammatory infiltration, (5) mucosal erosion and (6) granulation tissue. Reflux was graded in chronic (esophagitis grade 1, criteria 1 – 3) chronic active (esophagitis grade 2, criteria 4 alone or in combination with 1-3) and eroding ulcerating (esophagitis grade 3, criteria 5 or 6).
Results: 855 biopsy samples were obtained in 234 patients after a mean follow-up of 8.4 yrs (1 – 26). The average number of samples per patient was 4 (1 – 17). Five (2%) patients had no signs of esophagitis. 135 (57%) patients had esophagitis grade 1, 45 (19%) esophagitis grade 2, and 49(20%) grade 3. Specialized intestinal metaplasia compatible with Barrett's esophagus was found in 30 (13%) patients.
Conclusions: Most patients suffer from chronic esophagitis after dilatation therapy. 40% of the patients even show chronic active or ulcerating esophagitis. This may be associated with the risk of long-term GERD complications such as development of Barrett's esophagus.

In high-grade dysplasia in Barrett's esophagus MUC4 is increased and is associated with a pro-apoptotic Bax/Bcl-2 ratio

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MUC4 is a member of the membrane bound mucin family that protects the mucosa from damage by foreign bodies. It also acts as ligand for the receptor tyrosine kinase ErbB2 and has been reported to repress apoptosis. MUC4 is upregulated in several tumor types. The objectives of this study were i) to determine MUC4 mRNA levels during the course of neoplastic progression of Barrett's esophagus, and ii) to determine its association with mRNA levels of pro-apoptotic Bax and anti-apoptotic Bcl-2. Ninety-five biopsies from 37 patients diagnosed with Barrett's esophagus (mean age: 65 years, 20 males, mean length BE segment: 5.7 cm) were obtained during routine endoscopy from esophageal squamous epithelium (n = 37), Barrett's epithelium without dysplasia (BE, n = 37), Barrett's epithelium with high-grade dysplasia (HGD, n = 6) and adenocarcinoma (ADC, n = 15). Histological evaluation was performed independently by two experienced pathologists. The mRNA levels of MUC4, Bax and Bcl-2, and as a reference beta-actin, were determined by semi-quantitative RT-PCR. Compared to BE, MUC4 mRNA levels were significantly lower in normal squamous epithelium (mRNA levels relative to beta-actin in BE: 0.63 : 1.08, p=0.01), whereas levels were significantly elevated in HGD (0.63: 1.27, p=0.037) and in ADC (0.63: 1.16, p = 0.037). An association between MUC4 and inhibition of apoptosis was not found. In contrast, in HGD the Bax/Bcl-2 ratio showed a two-fold increase compared to BE (ratio 1.71 versus 0.83, p=0.04).
Conclusion: MUC4 mRNA levels are elevated in BE with HGD and in ADC. In contrast to animal studies where MUC4 overexpression was clearly associated with inhibition of apoptosis, upregulation of MUC4 in Barrett's esophagus with HGD is associated with promotion of apoptosis. This suggests that MUC4 in esophageal adenocarcinoma may have a protective effect against malignant transformation.

The role of the *Helicobacter pylori* outer membrane proteins AlpA and AlpB in the colonization of the guinea pig stomach

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Helicobacter pylori expresses several putative outer membrane proteins (OMPs) which may contribute to adherence to the gastric epithelium, but their role in gastric colonization by H. pylori is still poorly understood. The aim of this study was to determine the role of four individual OMPs (AlpA, AlpB, OipA and HopZ) in gastric colonization using a guinea pig model of H. pylori infection. Isogenic alpA, alpB, hopZ and oipA mutants were created in the guinea pig-adapted H. pylori strain GP15, and guinea pigs were intragastrically inoculated with either the wild-type strain or single mutants alone, or with wild-type strain and mutant strain in a 1:1 ratio. Three weeks after infection, animals were dissected, and H. pylori colonization and antibody response were determined.
H. pylori was isolated from all animals infected with wildtype GP15, the hopZ mutant or the oipA mutant, but only from 5 out of 9 (P=0.18) and 1 out of 7 (P=0.02) animals infected with the alpA mutant or the alpB mutant, respectively. The alpA and alpB mutants were also outcompeted by the wild-type GP15 strain in 1:1 competition infections, whereas the hopZ and oipA mutants could still be isolated from the majority of animals coinfected with wild-type and mutant strains. This indicates that absence of AlpA or AlpB, but not of OipA or HopZ, leads to a selective disadvantage during gastric colonization. Anti-H. pylori antibody responses were observed in all infected animals, but the levels of antibody responses were significantly lower in the animals infected with either the alpA mutant or the alpB mutant (P=0.01 for both mutants).
Conclusion: The AlpA and AlpB, but not the OipA and HopZ OMPs play an important role in the colonization of the gastric mucosa by H. pylori, most likely by mediating adherence to the gastric mucosa.
Characterization of the receptors of individual H. pylori OMPs may provide further insights into mechanisms allowing H. pylori colonization of the human gastric mucosa.

Polymorphism in the Interleukin 12B Gene in Colitis Susceptible Mice Affects Formation of Biologically Active IL-12 heterodimers.

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Crohn's disease as well as various experimental colitis models are characterized by increased expression of IL-12. What underlies these high IL-12 responses is unknown. IL-12 is a 70kDa heterodimeric cytokine formed by a p35 and a p40 chain. In a previous genetic analysis of susceptibility to TNBS-induced colitis we found strong linkage with a region on chromosome 11 harboring the gene encoding p40 (*IL12B)*. In the present study we sought to define the responsible mutation and molecular mechanism. First, we found that serum levels of biologically active IL-12 p70 are dramatically higher in colitis susceptible SJL/J than in resistant C57BL/6 mice ($P<0.0001$) after systemic challenge with LPS, whereas levels of IL-12 p40 did not differ between strains. Sequencing of *IL12B* revealed two polymorphisms in the coding region that give rise to non-conserved amino-acid substitutions. These substitutions are predicted to affect the affinity of the p40 chain to p35 to form heterodimers, and therefore provide a likely explanation for the observed strain differences in p70 but not in p40 secretion. To address this possibility, we generated bicistronic retroviral vectors containing the p40 gene derived from either SJL/J or from C57BL/6 linked to the p35 gene. Production of IL-12 p70 and p40, expressed as the p70/p40 ratio, was determined in supernatants from virally infected cells. We found that the p70/p40 ratio in cells infected with constructs derived from the colitis-susceptible SJL/J mice was significantly higher than in clones derived from the C57BL/6 strain in several independent experiments (mean ± SD = 53.7 ± 7.3 versus 22.7 ± 4.8; $P <0.001$). These findings provide strong evidence that the two polymorphisms in the coding region of *IL12* influence the formation of biologically active p70 dimers; in addition, they suggest that these polymorphisms acting through their effect on the IL-12 p70 response are responsible for the observed linkage and susceptibility to colitis.

The cholinergic anti-inflammatory pathway mediates the severity of experimental acute pancreatitis in mice

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The nervous system, through the vagus nerve, can downregulate inflammation by decreasing the release of TNF-α by LPS stimulated macrophages. This anti-inflammatory effect of the vagus nerve is mediated by an interaction of acetylcholine, the principle neurotransmitter of the vagus nerve, with macrophage cholinergic nicotine receptors expressing the α7 subunit. In three different studies, acute pancreatitis was induced by 12 hourly intraperitoneal injections of the cerulein; all mice were sacrificed immediately thereafter. Before the induction of acute pancreatitis, the cholinergic anti-inflammatory pathway was inhibited by a left sided cervical vagotomy (vs sham surgery) or by pre-treatment with hexamethonium, a peripheral nicotine receptor blocker (vs vehicle). In separate experiments the pathway was stimulated by pre-treatment of mice with the nicotinic acetylcholine receptor α-7 agonist GTS-21 (vs vehicle). Severity of acute pancreatitis was assessed by measuring serum amylase and lipase, pancreatitis histology, myeloperoxidase (MPO), and pro- and anti-inflammatory cytokine levels. Mice subjected to left cervical vagotomy or hexamethonium treatment had higher levels of plasma amylase and lipase as well as histopathological changes, pancreas edema, plasma IL-6 and pancreatic MPO content ($P<0.05$ vs sham surgery or vehicle). Conversely, mice pretreated with GTS-21 showed an attenuation of all parameters of pancreatitis severity ($P<0.05$ vs vehicle). The cholinergic anti-inflammatory pathway plays an important role in mediating acute pancreatitis severity in mice. This indicates that vagus nerve pathways function to control excessive local inflammation during pancreatitis. These data provide the first evidence pointing towards a crucial role for the cholinergic anti-inflammatory pathway during experimental acute pancreatitis.

Effect of gene promoter polymorphisms on mucosal TNF-α and matrix metalloproteinase-2 and -9 protein production in patients with inflammatory bowel disease

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In patients with inflammatory bowel disease (IBD), i.e., Crohn's disease (CD) and ulcerative colitis (UC), pro-inflammatory TNF-α and degradative Matrix MetalloProteinase (MMP)-2 and -9 protein levels are increased. We studied the impact of TNF-α -308 G/A, MMP-2 -1575 G/A and -1306 C/T, MMP-9 -1562 C/T gene promoter single nucleotide polymorphisms (SNP), determined by sequence analysis confirmed RFLP or tetra-primer ARMS-PCR, on protein production *ex vivo*. Mucosal explants were prepared from surgically resected intestinal tissue (11 CD, 9 UC) and cultured for 72 hrs. Macroscopically normal mucosal explants from 18 colorectal cancer patients were used as controls. Proteins in supernatant were measured by ELISA. Among patients with UC a significantly higher proportion was carrier of at least one mutant -1575 MMP-2 allele compared to controls (63 vs 18 %, P=0.04), while CD showed a non-significant increase in carrier frequency (36%). Identical results were obtained in case of MMP-2 -1306 SNP, confirming complete linkage disequilibrium between both polymorphism sites. No difference in distribution of MMP-9 -1562 alleles could be discerned with a mean mutant carrier frequency of 31%. The production of MMP-2 was similarly increased in UC and CD vs controls (median 26.7 vs 14.1 ng/mg, P≤ 0.001), as was observed for MMP-9 (2.5 vs 1.1 ng/mg, P≤ 0.01), but independent of genotype. A larger non-significant proportion of patients with IBD was carrier of at least one mutant allele at TNF-α -308 (37 vs 18 %), but protein production was independent of group and genotype. With respect to all three genes, the control population was in Hardy-Weinberg equilibrium. In summary, the carrier frequency of the mutant alleles at loci MMP-2 -1575, -1306, TNF-α -308 but not MMP-9 -1562 is increased in UC and CD patients. No relation between genotype and protein production could be discerned, stressing the importance of other regulatory mechanisms of inflammation in IBD.

Conjugated but not Unconjugated Bile Acids Induce Time-Dependent Increases in Proliferation in Barrett's Esophagus Ex Vivo Cultures

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Acid and/or bile variably alter cellular proliferation in Barrett's esophagus (BE) in a dynamic fashion predisposing to dysplasia and adenocarcinoma. We investigated the effect of bile acids on cell proliferation in BE and assessed mechanism(s) involved.
Organ cultures of biopsies from squamous esophageal epithelium, BE and duodenum were exposed to a 1-h pulse (at pH 7.4 or 3.5) with 1 mM of a bile acid mixture [cholic acid (CA) 40%, chenodeoxycholic acid (CDCA) 40% and deoxycholic acid (DCA) 20%, conjugated with glycine (75%) or taurine (25%)], or the same bile acids in unconjugated form. After the pulse, tissue samples were incubated in normal media for another 23 h at pH 7.4. Proliferation was assessed by proliferating cell nuclear antigen (PCNA) expression. PCNA and protein kinase C (PKC) isoform expression were determined by immunoblotting. Uptake of bile acids in BE was measured using ^{3}H labeled taurine-conjugates of CA and CDCA.
Conjugated bile acids (pH 7.4) increased proliferation (µg PCNA/mg protein) in BE from 58±12 to 131±18 at 1-h ($p<0.05$) and 212±24 at 24-h ($p<0.01$), but not in squamous esophagus or duodenum. At pH 3.5, conjugated bile acids increased proliferation from 61±13 to 126±13 at 1-h ($p<0.05$), which normalized at 24-h (68±13). Incubation with unconjugated bile acids at pH 7.4 or 3.5 had no effect. PKCε was over-expressed in BE in response to conjugated bile acids at 1-h (ratio: 1.53±0.12; $p<0.05$) and 24-h (2.32±0.18; $p<0.01$). At pH 3.5, there was a trend towards increased expression of PKCε at 1-h (1.42±0.11; $p=0.06$), but not at 24-h (0.97±0.06). Incubation of BE with ^{3}H taurine-conjugated CA and CDCA showed no conjugated bile acid uptake.
Conclusion**:** Without entering the cells, conjugated bile acids at neutral pH induce cell proliferation in BE, in association with induction of PKCε. In an environment of acid suppression, reflux of conjugated bile acids may predispose to dysplasia in BE via their effect on cell proliferation.

The NikR regulatory protein governs transcriptional regulation of NixA-mediated nickel-uptake in *Helicobacter pylori*

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Helicobacter pylori produces large amounts of the the nickel-containing metalloenzyme urease, which plays an essential role in virulence of this human pathogen. To obtain nickel *H. pylori* requires efficient acquisition systems, but also mechanisms to maintain cytoplasmic nickel homeostasis to avoid cytotoxicity. The aim of this study was to determine the roles of the NikR protein as regulator of nickel homeostasis and NixA as nickel-uptake system.

Growth of *H. pylori* reference strain 26695 wildtype, *nikR* mutant, *nixA* mutant and a *nikR-nixA* double mutant was determined in Brucella media supplemented with $NiCl_2$ up to 1 mM. Transcription of the *nixA* gene was analyzed by Northern hybridization. Protein expression was determined by urease activity measurement and SDS-PAGE, while gel mobility shift assays and DNAse footprinting with the *nixA* promotor were used to characterize the interaction of NikR with the *nixA* promotor.

The parental *H. pylori* strain 26695 was resistant to $NiCl_2$ concentrations of up to 750 µM, whereas an isogenic *nikR* mutant displayed a significant increase in nickel-sensitivity. Inactivation of the nickel-transporter gene *nixA* abolished the nickel-sensitivity of the *nikR* mutant. Transcription of the *nixA* gene was nickel-responsive in the wildtype strain, while in the *nikR* mutant the *nixA* gene was constitutively transcribed. Direct NikR-mediated regulation of the *nixA* promotor was confirmed using DNAse footprinting. Finally, nickel induction of urease activity was dependent on NikR and nickel, but nor on *nixA*.

Conclusion: The NikR protein plays a central role in nickel-uptake, allowing nickel-uptake via *nixA* only when nickel is scarce. This regulatory pattern is similar to that described for iron via the Fur protein. The presence of this nickel-responsive system mediating regulation of the essential virulence factor urease may allow for the development of new therapeutic compounds for treatment of *H. pylori* infection.

Protective effect of exogenous alkaline phosphatase in the inflammatory response in secondary peritonitis

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Lipopolysaccharide (LPS) is the most potent endotoxin and as such a major contributor to the production and release of cytokines (e.g. TNF-α, IL-6 and MCP-1) in secondary peritonitis. Once dephosphorylated by alkaline phosphatase (AP) LPS cannot elicit a cytokine response. The effect of administration of calf intestinal AP (CiAP) on inflammation and survival was assessed in a murine cecal ligation and puncture model (CLP).
C57BL/6 mice were divided into 5 groups: (A) CLP+CiAP administered 5 min. pre puncture (prevention), (B) CLP+CiAP 15 min. post puncture (early treatment), (C) CLP+saline (S) (pos. control), (D) sham+CiAP and (E) sham+S (neg. controls). CiAP was given 0.16 IU/gr (50-100x plasma level). Mice (n=8 /group/time point) were sacrificed after 30 min, 4, 6, 8 or 24 hours. In addition a survival study (n=13-19 /group) was performed up to 72 hours. Parameters investigated were: inflammatory cells and colony forming units (CFU) in peritoneal lavage fluid (PLF), TNF-α, IL-6, and MCP-1 in both plasma and PLF, AST and ALT in plasma and survival.
The number of inflammatory cells and the aerobic and anaerobic CFUs in PLF were elevated after CLP (A-C) compared to sham (D&E) ($p<0.05$), without differences between CLP groups. Increased TNF-α, IL-6 and MCP-1 levels were found both in plasma and in PLF after CLP (A-C) ($p<0.01$). These levels were reduced both in plasma and PLF in the CiAP groups (A&B) compared to saline (C) ($p<0.05$). AST and ALT are raised after CLP (A-C) ($p<0.01$), with significantly lower levels in group A then in C ($p<0.05$), indicating less secondary hepatocellular damage. Finally, survival was decreased in all CLP groups, without showing an effect of CiAP.
In this secondary peritonitis model CiAP reduces the inflammatory response by decreasing the LPS mediated cytokine response, both locally and systemically. CiAP as prophylaxis decreases secondary hepatocellular damage. No effect on survival could be demonstrated.

Microarray analysis implicates calprotectin as potential novel tumor marker for high-grade dysplasia in Barrett's esophagus

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Patients with Barrett's esophagus (BE) have a significantly increased risk of developing esophageal adenocarcinoma. Carcinoma develops via a multistep process in which malignant degeneration is preceded by dysplastic changes of the metaplastic mucosa. Tumor markers for high-grade dysplasia (HGD) could enhance the detection of early lesions in BE. The objective of this study was to identify these markers. Jumbo biopsy samples from BE without dysplasia and with HGD were obtained from a 53-yr old male patient during routine endoscopy. Biopsies were divided in two equal parts. One part was evaluated for the presence or absence of dysplasia and the other part was used for microarray analysis, using the Atlas human 12K array. The mRNA expression pattern of the BE sample without dysplasia was compared to that of the HGD sample. Microarray results were confirmed by semi-quantitative RT-PCR in biopsies from patients with BE without dysplasia (n = 22) and with HGD (n = 5) obtained during routine endoscopy from 22 patients (13 male, mean age 68.1 years). Compared to BE, HGD showed >2-fold difference in mRNA levels for 866/12000 genes (7%). Of these 866, 33 displayed a >10-fold difference. For these 33 genes, semi-quantitative RT-PCRs were performed in a larger panel. Two genes were significantly upregulated in HGD, calgranulin A (relative expression in normal BE 0.79 vs. 1.75 in HGD, p = 0.017 Mann-Whitney U-test) and calgranulin B (relative expression: 0.83 vs. 1.81, p = 0.022). For the other 31 genes, differences in mRNA levels between HGD and BE were detected, but did not test significant in this large panel of samples.
Conclusion: The inflammatory proteins calgranulin A and B are potential new tumor markers for high-grade dysplasia in Barrett's esophagus. These proteins, both subunits of the calprotectin complex, may play a role in the development of a more malignant phenotype of Barrett's esophagus, a process in which inflammation may be involved.

Quality of life after palliative treatment for esophageal carcinoma: a longitudinal prospective comparison between stent placement and single dose brachytherapy

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Metal stent placement and single dose brachytherapy are commonly used treatment modalities for the palliation of inoperable esophageal carcinoma. We investigated generic and disease-specific health-related quality of life (HRQoL) after these palliative treatments.
Patients with dysphagia from inoperable esophageal carcinoma were randomized to placement of a covered Ultraflex stent (n=108) or single dose (12 Gy) brachytherapy (n=101). We obtained longitudinal data on disease-specific (dysphagia score, EORTC OES-23, visual analogue pain scale) and generic (EORTC QLQ-C30, EuroQol-5D) HRQoL at monthly home visits by a specially-trained research nurse. We compared HRQoL between the two treatments and analyzed changes in HRQoL during follow-up.
Dysphagia improved more rapidly after stent placement than after brachytherapy, but long term relief of dysphagia was better after brachytherapy. For generic HRQoL, there was an overall significant difference in favor of brachytherapy on several functional scales of the EORTC QLQ-C30 (role, emotional, cognitive and social) ($p<0.05$). Generic HRQol deteriorated over time on all functional scales of the EORTC QLQ C-30 and Euroqol-5D, in particular physical and role functioning (-23 and -24 on a 100 points scale during 0.5 years of follow-up) in both treatment groups. This decline was more pronounced in the stent group. In contrast, except for the dysphagia and eating scales, no major changes during follow-up were seen for disease-specific HRQoL. Self-reported pain levels remained stable during follow-up in both treatment groups.
Conclusions: Treatment with single dose brachytherapy gave better overall scores on HRQoL scales compared to stent placement for the palliation of esophageal cancer. Generic HRQol scales were more responsive in measuring patients' functioning and well-being during follow-up. Pain management was adequate during follow-up.

Clinical significance of immunohistochemically detected micrometastases in histologically negative lymph nodes of patients with adenocarcinoma of the distal oesophagus or gastric cardia

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Lymphatic dissemination is the most important prognostic factor in patients with oesophageal carcinoma. In contrast, the clinical significance of immunohistochemically detected lymph node micrometastases in histologically node-negative (pN0) patients is still debated. The aim of this study was to analyse the clinical implications of nodal micrometastases in type I and II tumours and to determine the benefits of an extended transthoracic resection for patients with early lymphatic dissemination.
From a consecutive series of 79 patients who underwent a transthoracic resection, all 22 patients with pN0 adenocarcinoma were included in this study. A total of 636 lymph nodes from these patients were examined for the presence of micrometastases by immunohistochemical analysis with the monoclonal anti-epithelial-cell antibodies BerEP4, AE1/AE3 and CAM5.2.
Lymph node micrometastases were detected in six of the 22 patients (27%). They were found in 17 of the 636 lymph nodes (3%). Lymph nodes containing micrometastases were widely distributed, but the truncal nodes were most frequently involved. The presence of micrometastases was not significantly correlated with any clinicopathological parameters (e.g. depth of tumour invasion, and tumour differentiation grade). However, an association was found between the presence of nodal micrometastases and the development of distant metastases ($p=0.02$), locoregional recurrences ($p=0.09$) and a reduced overall survival ($p=0.02$).
Conclusions: Immunohistochemically detected micrometastases in lymph nodes have prognostic significance for patients operated upon for adenocarcinoma of the oesophagus or gastric cardia. Even minimal lymphatic dissemination is associated with a high incidence of systemic recurrence. Moreover, extensive transthoracic resection does not prevent locoregional recurrences. Therefore, we feel that for these early disseminated carcinomas, systemic (neo-) adjuvant treatment is needed in acquiring long-term survival.

Colorectal Neoplasia in Veterans is Associated with Barrett's Esophagus but not with use of Proton-Pump Inhibitors (PPIs) or Aspirin/NSAIDs

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An association between Barrett's esophagus (BE) and colorectal neoplasia has been suggested, but is still controversial. We investigated whether BE was associated with an increased risk of colorectal neoplasia, and, if so, whether BE was an independent risk factor or dependent on the use of PPIs or aspirin/NSAIDs.
We performed a case-control study, where we matched 268 veterans with histologically-proven BE (mean length: 2.0 cm, range: 0.5-10 cm, all intestinal metaplasia) with 268 controls without BE. Controls had undergone upper GI endoscopy close (± 14 days) to the time of the corresponding case. Colonoscopy was performed within 6 months of the upper GI endoscopy. Patient characteristics (age, gender, ethnicity, and body mass index [BMI]), tobacco or alcohol use, use of PPIs and aspirin/NSAIDs, and findings at colonoscopy were recorded.
Mean age was not different (BE group vs. controls: 66 ± 11 vs. 64 ± 12 years). The majority were men (99% vs. 97%) and white (74% vs. 72%). Mean BMI was similar (28 ± 6 and 29 ± 6) as was smoking (40% vs. 34%), but alcohol use was more common in the BE group (66% vs. 46%, $p< 0.001$). BE patients used more often PPIs (54% vs. 25% ($p< 0.001$), but less often aspirin/NSAIDs (50% vs. 61%, $p=0.007$). Colorectal adenomas or carcinoma were present in 160/268 (60%) patients of the BE group and in 105/268 (39%) controls ($p<0.001$). The total number of polyps (BE group vs. controls: 1.8 vs.1.9) and the mean size of the polyps (0.60 vs. 0.55 mm) were similar in those with polyps. Increasing age (OR 1.23 per decade, 95% CI [1.02, 1.49]), use of alcohol (OR 1.76: 95% CI [1.19, 2.60]), and BE (OR 1.93: 95% CI [1.29, 2.91]) were associated with an increased risk of developing colorectal neoplasia, when statistically adjusted in multivariate analysis.
Conclusion: Our results suggest that veterans with BE are at an increased risk of developing colorectal neoplasia. This association is independent from the use of PPIs and aspirin/NSAIDs.

Barrett's esophagus is associated with an increased epithelial inflammation.

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Intestinal metaplasia in Barrett's esophagus (BE) is thought to be an adaptive response to prolonged duodeno-gastro-esophageal reflux. Endoscopically, BE is often free from the characteristic inflammatory signs associated with reflux esophagitis (RE) and BE may therefore also be associated with a decreased microscopic inflammatory response. In this study, we investigated whether the inflammatory response in BE is indeed decreased and distinct from the inflammatory response observed in RE.
A total of 76 biopsies, 50 from 16 patients with histologically confirmed BE (mean age 70.8 ± 14 years, 66% male), 20 biopsies from 20 patients with RE (age 61.8 ± 11.6; 71% male) and 6 biopsies from 6 controls with macroscopically non-inflamed esophagus were analyzed by immuno-histochemistry using mAbs against macrophages/monocytes, cytotoxic T-cells, mast cells and B-cells. Inflammatory cells were visualized in serially sectioned slides, and the mean number of cells were counted in 10 representative microscopic fields and given as average cell numbers per microscopic field.
The numbers of all inflammatory cell types were significantly higher in columnar epithelium of BE compared to the squamous epithelium of RE and controls. A significant increase of inflammatory cell counts was also observed in RE compared to controls, but only for macrophages-/monocytes and mast cells. Mast cells were the predominant inflammatory cell type in BE, with a 5-fold and 10-fold increase in BE compared to RE and controls, respectively.
Conclusion: The replacement of squamous epithelium by specialized intestinal epithelium in BE does not lead to a decreased inflammatory response, despite the absence of hallmarks of inflammation at endoscopy. Moreover, the different cellular infiltration in BE compared to RE suggests that stimuli other than the chemical injury play a role in the maintenance of inflammation in BE. Finally, a sustained inflammation may contribute to a malignant tendency in BE.

Initial and Long-term Outcome of Biliary Bypass Surgery in Periampullary and Pancreatic Carcinoma

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Controversy remains on the palliative treatment of biliary obstruction. Endoscopic stent placement is effective for short term relief of jaundice and early complications are uncommon. However, stent exchanges are needed frequently and cause considerable morbidity. Surgical bypass procedures can offer optimal long-term palliation of obstructive jaundice but are associated with higher morbidity and mortality. The aim of this study was to analyze initial morbidity and mortality and long-term outcome after biliary bypass surgery for periampullary and pancreatic carcinoma.
From 1992 to 2003, 277 patients underwent a surgical biliary bypass. Perioperative parameters and the incidence of readmissions were analyzed to assess initial and long-term outcome.
The overall complication rate was 29%. The rates for severe complications were 1% for anastomotic leakage, 3% for abdominal hemorrhage and 3% for abdominal abscesses. Three percent underwent a relaparotomy during initial stay. Median hospital stay was 10 days and hospital mortality was 3%. 57% of patients were readmitted: 16 (6%) patients were readmitted for indications related to the biliary bypass, 12 (4%) for surgery-related indications, 126 (45%) for disease-related indications and 24 (9%) for indications not related to the disease. Twenty three (9%) patients underwent a relaparotomy during a readmission, mainly for gastrointestinal obstruction due to tumor ingrowth. Median and 3-year survival was 7.4 months and 3%.
Surgical bypass procedures are associated with a relative low complication rate and acceptable mortality. The overall readmission rate was high, mainly due to readmissions indicated for disease-related complications. The incidence of readmissions indicated for complications related to the biliary bypass and to surgery was low. In conclusion, a surgical biliary bypass is a safe and effective procedure to treat and prevent biliary obstruction in patients with periampullary and pancreatic carcinoma.

Genetic polymorphisms in detoxification enzymes and colorectal cancer risk

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Colorectal cancer (CRC) is one of the most common malignancies in the Western world and has been associated with genetic and lifestyle factors. Individual susceptibility to CRC may be partly due to genetic polymorphisms in detoxification enzymes. These genetic polymorphisms may result in variations in detoxification activities, which subsequently might influence the levels of toxic/carcinogenic compounds. To determine whether genetic polymorphisms in detoxification enzymes predispose to the development of CRC, 370 patients with sporadic CRC and 412 healthy controls were genotyped for polymorphisms in glutathione S-transferases (GSTA1, GSTM1, GSTP1 and GSTT1), microsomal epoxide hydrolase (EPHX1), NAD(P)H oxidase p22phox, NAD(P)H:quinone oxidoreductase (NQO1) and UDP-glucuronosyl transferases (UGT1A1, UGT1A6, UGT1A7 and UGT1A8). Patients and controls were all of Caucasian origin. DNA was isolated from either blood or tissue and tested by polymerase chain reaction followed by restriction-fragment-length-polymorphism analyses. Logistic regression analyses showed significant age- and gender-adjusted risks for CRC associated with variant genotypes of NQO1 (OR 1.54, 95% CI 1.02-2.33), UGT1A6 (OR 1.52, 95% CI 1.01-2.27) or UGT1A7 (OR 2.23, 95% CI 1.19-4.18), whereas no associations were found between CRC and the other polymorphic genes as mentioned above. In conclusion, these data suggest that the presence of variant genotypes of NQO1, UGT1A6 or UGT1A7 might enhance susceptibility to CRC.

Concordance of serologic and genetic markers in twins with inflammatory bowel disease

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The inflammatory bowel diseases (IBD) Crohn's disease (CD) and ulcerative colitis (UC) are complex polygenic diseases of unknown origin. CARD15 has been identified as the first gene associated with CD. Antibodies to *Saccharomyces cerevisiae* (ASCA) are found in about 60% of CD patients and peri nuclear anti neutrophil cytoplasmic antibodies (pANCA) are associated with UC. To determine whether genetic factors are implicated in the pathogenesis of serologic markers, we studied ASCA and pANCA and CARD15in mono- and dizygotic twins with at least one member affected by IBD. In total, 36 twin pairs were collected at two centers. The monozygotic twins (n=14) consisted of 14 CD, 6 UC and 8 unaffected. The dizygotic twins (n=22) included 18 CD, 5 UC, 2 indeterminate colitis (IC) and 19 unaffected. There were no mixed (CD and UC) twin pairs. ASCA and pANCA were determined by a standardized ELISA and indirect immunofluorescence, respectively. Subjects were genotyped for the CARD15 variants Arg702Trp, Gly908Arg and Leu1007InsC using PCR-RFLP. Groups were compared using Chi-square test or Fisher's Exact. Concordance for disease in mono- and dizygotic twins was respectivily 43%(6/14) and 14%(3/22). Concordance for ASCA+ in mono- and dizygotic twins was 57%(4/7) and 0%(0/10)(p=0.015). ASCA were found in 63%(20/32) of CD patients and in one, unaffected monozygotic sibling of CD. Only 3/72(4.2%) subjects were pANCA positive: 1UC patient and 2 unaffected siblings of UC patients. The prevalence of CARD15 was 38%(12/32) in CD patients, 27%(3/11) in UC patients and 22%(6/27) in unaffected siblings.
Conclusions: Monozygotic twins are not only more concordant for disease, but also for ASCA. These results give additional evidence for a genetic basis of ASCA. Except for UC, the prevalence of CARD15 in this cohort was similar to previous reports. Numbers were too small for pANCA in this study population to draw reliable conclusions. Collaborative efforts are needed for further investigation.

TPMT polymorphisms in a Dutch population of inflammatory bowel disease patients

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Azathioprine (AZA) is effective in treatment of inflammatory bowel disease (IBD), but toxicity concerns have restricted its use. Individual responses to AZA are thought to be associated with thiopurine S-methyltransferase (TPMT) activity, due to genetic polymorphisms. TPMT enzyme catalyzes S-methylation of cytotoxic thiopurine drugs like AZA. High TPMT activity corresponds with two wild-type (wt) alleles, intermediate levels with one mutant allel, and no activity with two mutant alleles. Here we studied frequency of TPMT polymorphisms in a Dutch IBD population and their association with adverse effects.
We determined TPMT genotype of 133 IBD patients; 65 were treated in our clinic, and 68 DNA samples derived from our archive. Genomic DNA was isolated from blood and polymorphisms TMPT*2, *3A, *3B, and *3C were identified after polymerase chain reaction (PCR) and endonuclease digestion.
Of 65 patients 11% (7 patients) had mutant alleles: 4 patients had TPMT*3A (1 patient was homozygous, who required hospitalisation due to severe leukopenia), and 3 patients had *3C mutation. Five of them (71%) were treated with AZA and all developed adverse effects. Two patients stopped AZA therapy, because they developed fever, rash, or leukopenia. Three patients received lower doses (50-75 mg) of AZA, due to leukopenia development (2 patients) or abnormal liver function. Out 68 archive samples, we observed 9 mutations (13%); 1 patient had TPMT*2, 3 patients had *3A, 3 patients had *3B, and 2 patients had *3C mutations. In this group 47 patients were treated with AZA, and 22 (47%) developed adverse effects.
Conclusions: In 12% of our study population TPMT mutations were found, which is in accordance with previous reports. However, 71% of the affected patients, being monitored after receiving AZA, displayed serious side effects. In conclusion, determining TPMT polymorphism is important to identify IBD patients at risk for severe myelosuppression when treated with standard AZA doses.

Segmental or radical colonic resection for Crohn's colitis?

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Segmental colonic resection is the most performed procedure in patients with Crohn's colitis. A large proportion of this group will undergo total (procto)colectomy. The aim of this study was to evaluate the outcome after segmental resection and try to identify potential risk factors for re-resection.
Data on initial colonic resection and postoperative recurrence were retrospectively evaluated for patients who underwent resection for Crohn's colitis in our hospital between 1988 and 2000. Patient and treatment related parameters were assessed as possible risk factors for recurrence.
A total of 110 patients underwent resection for Crohn's colitis. Six patients were lost to follow-up and 13 patients had primary proctocolectomy and were therefore excluded for analysis. Of the remaining 91 patients (31.9% male), median follow-up was 62 months (2-157). Sixty-five patients (71.4%) had one segmental colonic resection, 26 (28.6%) two or more segmental colonic resections of whom 17 (65.4%) finally ended up total (procto)colectomy. Female sex and left sided initial resection were independent significant risk factors for re-resection (multivariate analysis). For patients with re-resection (n=26), smoking doubled the period between first operation and re-resection ($P<0.05$, Mann-Whitney). Kaplan-Meier survival analysis for the entire group (n=91) showed that, although not significant, higher body mass index, younger age at initial resection and smoking tended to extend the reoperation free survival.
Conclusion: After segmental resection for Crohn's colitis, 28.6% of patients underwent re-resection and only 17 patients (18.7%) finally underwent total (procto)colectomy. Limited resection is therefore justified. Female sex and initial left sided resection are associated with increased risk of re-resection. Smoking has a protective effect.

Alfabetische lijst van standhouders voorjaarscongres 2004

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Cook Nederland BV	K3
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