Programma voorjaarsvergadering 16 en 17 maart 2006

Nederlandse Vereniging voor Gastroenterologie

Sectie Gastrointestinale Endoscopie
Netherlands Society for Parenteral and Enteral Nutrition
Sectie Neurogastroenterologie en Motiliteit
Sectie Experimentele Gastroenterologie
Sectie Kindergastroenterologie
Sectie Endoscopie Verpleegkundigen en Assistenten
Vereniging Maag Darm Lever Verpleegkundigen

Nederlandse Vereniging voor Hepatologie

Nederlandse Vereniging voor Gastrointestinale Chirurgie

Nederlands Genootschap van Maag-Darm-Leverartsen

NH KONINGSHOF VELDHOVEN

INHOUDSOPGAVE pag.

Belangrijke mededeling
aan alle deelnemers aan de voorjaarsvergadering 3

Voorwoord 4
Programma cursorisch onderwijs in mdl-ziekten 15 en 16 maart 2006 5
Schematisch overzicht donderdag 16 maart 2006 6
Schematisch overzicht vrijdag 17 maart 2006 7

DONDERDAG 16 MAART 2006

middagprogramma
Vrije voordrachten Vereniging voor Gastrointestinale Chirurgie 8
Vrije voordrachten Sectie Neurogastroenterologie en Motiliteit 12
Vrije voordrachten Netherlands Society of Parenteral and Enteral Nutrition 15
Vrije voordrachten Nederlandse Vereniging voor Hepatologie 17
Symposium NVH 'Interventions in Hepatology' 20

avondprogramma
Diner in Genderzaal v.a. 18.00 uur
Presidential Selection, plenaire sessie v.a. 20.00 uur in de **Diezezaal** 21

VRIJDAG 17 MAART 2006

ochtendprogramma
Casuïstiek voor de clinicus 23
Vrije voordrachten Sectie Gastrointestinale Endoscopie 23
Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie 26
Vrije voordrachten Sectie Experimentele Gastroenterologie 29
International Teaching Session 31
Programma Sectie Endoscopie Verpleegkundigen en Assistenten 38

middagprogramma
Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie Brabantzaal 32
Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie Baroniezaal 34
Vrije voordrachten Sectie Experimentele Gastroenterologie 36
Vervolg programma Sectie Endoscopie Verpleegkundigen en Assistenten 38

Abstracts voorjaarscongres 39-165
Plattegrond expositie en overzicht aanwezige bedrijven 166-168
Aanmeldingsformulieren lidmaatschappen 169-175

Belangrijke mededeling
over de aanwezigheid van farmaceutische industrieën

Aan alle deelnemers aan de voorjaarsvergadering

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

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

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

Het bestuur van de NVGE

VOORWOORD

Hierbij treft u het volledige programma aan van de voorjaarsvergadering 2006 te Veldhoven.

Het programma zal donderdag 16 maart van start gaan om 13.00 uur. Zoals bekend ligt tijdens de voorjaarsvergadering vooral het accent op vrije voordrachten. Op donderdag-middag zijn er vrije voordrachten van de Nederlandse Vereniging voor Gastrointestinale Chirurgie, vrije voordrachten van de Sectie Neurogastroenterologie en Motiliteit, de Netherlands Society of Parenteral and Enteral Nutrition en de Nederlandse Vereniging voor Hepatologie. De laatste verzorgt op donderdagmiddag tevens een symposium getiteld: 'Interventions in Hepatology'

De plenaire donderdagavond sessie met de Presidential Selection vindt dit keer plaats in de **Diezezaal**, aanvang 20.00 uur**.** Alle congresdeelnemers worden van harte uitgenodigd bij deze sessie aanwezig te zijn!

Op vrijdag zijn er veel sessies met vrije voordrachten van Nederlandse Vereniging van Gastroenterologie, de Sectie Gastrointestinale Endoscopie en de Sectie Experimentele Gastroenterologie. De laatste organiseert v.a. 10.30 uur in de Parkzaal tevens de traditionele 'International Teaching Session'.
In de Diezezaal wordt door de Sectie Endoscopie Assistenten en Verpleegkundigen een eigen programma verzorgd, waar ook de leden van de Vereniging voor Maag Darm Lever Verpleegkundigen van harte welkom zijn!

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

Dr. P.D. Siersema,
vice-voorzitter, waarnemend secretaris

Tijdstippen diverse ledenvergaderingen tijdens voorjaarsvergadering:

Assistentenvereniging Touché (mdl-artsen i.o.)	16 maart, 12.15 uur - Zaal 82/83
Nederlandse Vereniging voor Hepatologie	16 maart, 15.00 uur - Parkzaal
Nederlandse Vereniging voor Gastroenterologie	16 maart, 21.00 uur - Diezezaal
Nederlands Genootschap van Maag-Darm-Leverartsen	17 maart, 12.00 uur - Zaal 81/82/83
Sectie Endoscopie Verpleegkundigen en Assistenten	17 maart, 11.30 uur – Diezezaal

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

Woensdag 15 maart 2006

voorzitter:	Dr. H.M. van Dullemen
20.30 – 20.55 uur	IBD, etiologie en epidemiologie in Nederland *Dr. M.G.V.M. Russel, MDL, Medisch Spectrum Twente*
20.55 - 21.20 uur	5-ASA; topicaal/oraal: bij wie nog? *Dr. R.A. van Hogezand, MDL, LUMC*
21.20 – 21.45 uur	Azathioprine in IBD: mechanism of action, long and short term side effects. *Dr. A.A. van Bodegraven, MDL, VUmc*
21.45 - 22.20 uur	Thiopurine: therapeutic drug monitoring *K.H.N. de Boer, MDL, VUmc*
22.20 – 22.30 uur	Discussie

Donderdag 16 maart 2006

voorzitter:	Prof. dr. C.J.J. Mulder
08.00 – 08.30 uur	Methotrexaat en Ciclosporine, doen wij het nog? *Dr. C.J. van der Woude, MDL,EMC*
08.30 – 09.00 uur	Steroïden: klassiek of topicaal (lokaal) *Dr. D.J. de Jong, MDL, UMCN*
09.00 – 09.30 uur	Geven we wel genoeg Infliximab? *Dr. D.W. Hommes, MDL, AMC*
09.30 – 10.00 uur	Osteoporose in IBD *Prof. dr. J.C. Netelenbos, Endocrinologie, VUmc*
10.00 – 10.30 uur	koffiepauze
voorzitter:	Dr. C.J.H.M. van Laarhoven
10.30 – 11.00 uur	Resecties bij IBD *Dr. C.J.H.M. van Laarhoven, HLK, St. Elisabeth Ziekenhuis*
11.00 - 11.30 uur	Fistelchirurgie bij M. Crohn *Prof. dr. R.J. Ploeg, HLK, UMCG*
11.30 – 11.45 uur	Probiotica / Antibiotica bij pouchitis *M.P. Gosselink, HLK, EMC*
11.45 – 12.10 uur	Pouchsurvival / complications *Prof. A. D'Hoore, Katholiek Universiteit Leuven, België*

Programma donderdag 16 maart 2006

DONDERDAG	BRABANTZAAL	BARONIEZAAL	PARKZAAL	DIEZEZAAL
13.00	Vrije voordrachten Nederlandse Vereniging voor Gastrointestinale Chirurgie p. 8	Vrije voordrachten Sectie Neurogastroenterologie en Motiliteit p. 12	Vrije voordrachten Nederlandse Vereniging voor Hepatologie p. 17	
15.00	Theepauze	Theepauze	Thee / ledenvergadering	
15.30	Vervolg Vrije voordrachten Nederlandse Vereniging voor Gastrointestinale Chirurgie p. 10	Vrije voordrachten Netherlands Society of Parental and Enteral Nutrition p. 15	**Symposium NVH 'Interventions in Hepatology'** p. 20	
17.00	Congresborrel expositiehal	Congresborrel expositiehal	Vervolg symposium tot 17.30	
18.00	Diner in Genderzaal	Diner in Genderzaal	Diner Genderzaal	Diner in de Genderzaal
20.00				**Presidential Selection** p.21
21.00				**Ledenvergadering NVGE**
22.30	Congresborrel Brabantzaal			

Programma vrijdag 17 maart 2006

VRIJDAG	BRABANTZAAL	BARONIEZAAL	PARKZAAL	DIEZEZAAL
08.30	Casuïstiek voor de clinicus *om 9.20 uur gevolgd door* Vrije voordrachten Sectie Gastrointestinale Endoscopie p. 23	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie p. 26	Vrije voordrachten Sectie Experimentele Gastroenterologie p. 29	
10.00	Koffiepauze	Koffiepauze	Koffiepauze	Ontvangst en koffie SEVA
10.30	Vervolg vrije voordrachten Sectie Gastrointestinale Endoscopie p. 24	Vervolg vrije voordrachten Nederlandse Vereniging voor Gastroenterologie p. 27	**International Teaching Session**, Sectie Experimentele Gastroenterologie p. 31	Programma Sectie Endoscopie Verpleeg-kundigen en Assistenten p. 38
12.00	Lunch in expositiehal	Lunch in expositiehal	Lunch in expositiehal	12.30 Lunch in expositiehal
13.30	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie p. 32	Vervolg vrije voordrachten Nederlandse Vereniging voor Gastroenterologie p. 34	Vervolg vrije voordrachten Sectie Experimentele Gastroenterologie p. 36	Vervolg programma Sectie Endoscopie Verpleeg-kundigen en Assistenten p. 38
15.00	Thee / einde programma	Thee / einde programma	Thee / einde programma	Einde programma

Nederlandse Vereniging voor Gastrointestinale Chirurgie **Brabantzaal**

12.30 Inschrijving, koffie

Voorzitters: J. Meijerink en M. Bemelmans

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

13.00 Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the oesophagus: five year survival of a randomized clinical trial (p. 39)
J.M.T. Omloo[1], S.M. Lagarde[1], J.B.F. Hulscher[1], J.B. Reitsma[2], P. Fockens[3], H. van Dekken[4], F.J.W. ten Kate[5], H. Obertop[6], H.W. Tilanus[6], J.J.B. van Lanschot[1], Depts of Surgery[1], Clinical Epidemiology and Biostatistics[2], Gastroenterology[3] and Pathology[5], Academic Medical Centre, Amsterdam and Depts of Surgery[6] and Pathology[4] at the Erasmus Medical Centre, Rotterdam, The Netherlands

13.10 Analysis of gene expression discovers pathways associated with hematogenous metastasis in patients with adenocarcinoma of the esophagus (p. 40)
S.M. Lagarde[1], P.E. Ver Loren van Themaat[2], P.D. Moerland[2], L.A. Gilhuijs-Pederson[2], F.J.W. ten Kate[3], P.H. Reitsma[4], A.H.C. van Kampen[2], A.H. Zwinderman[5], F. Baas[6], J.J.B. van Lanschot[1]. Depts of Surgery[1], Bionformatics[2], Pathology[3], Experimental Internal Medicine[4], Clinical Epidemiology and Biostatistics[5] and Neurogenetics[6], Academic Medical Center at the University of Amsterdam, The Netherlands

13.20 Surgical reintervention after antireflux surgery for gastro-esophageal reflux disease; a prospective cohort study in 130 patients (p. 41)
E.J.B. Furnee[1], W.A. Draaisma[1], H.G. Gooszen[1], A.J.P.M. Smout[2], I.A.M.J. Broeders[1], Department of Surgery[1] and Gastroenterology[2], University Medical Center Utrecht, The Netherlands

13.30 CT investigation in CD 117 revised gastrointestinal stromal tumours (GISTs) (p. 42)
S. Sassen, C.L.H. van Berlo, P.H.A. Nijhuis, S. Wouda[1]. Depts of Surgery and Pathology[1], VieCuri Medical Centre, Venlo, The Netherlands

13.40 Laparoscopic adjustable gastric banding less successfull without follow-up (p. 43)
W.W. *te Riele, M. Avci, B. van Ramshorst, Dept of Surgery, Sint Antonius Hospital, Nieuwegein, The Netherlands*

13.50 Assessment of viable tumor tissue attached to needle electrodes after local ablation of liver tumors (p. 44)
N. Snoeren[1] , M.C. Jansen[1] , A.M. Rijken[2] , R. van Hillegersberg[3] , J. Klaase[4] , G. Slooter[5] , S. Meijer[6] , E vd Linden[7], F.J.W. ten Kate[8], T.M. van Gulik[1]. Dept of Surgery[1] and pathology[8], Academic Medical Center, Amsterdam, Depts of Surgery, Amphia Hospital[2], Breda, University Medical Center, Utrecht[3], Medical Spectrum Twente, Enschede[4], Maxima Medical Center, Veldhoven[5], Free University Medical Center[6], Amsterdam and Dept of Radiology, Leiden University Medical Center[7], Leiden, The Netherlands

14.00 Liver volumetry plug and play: do it yourself with Image! (p. 45)
S.A.W.G. Dello[1], J.J.G. Slangen[1], R.M. van Dam[1], M.C.G. van de Poll[1], M.H.A. Bemelmans[1], J.W.M. Greve[1], R.G.H. Beets-Tan[2], S.J. Wigmore[3], C.H.C. Dejong[1], Depts of Surgery and Nutrition and Toxicology Research Institute Maastricht[1], Maastricht University, Dept of Radiology[2], University Hospital Maastricht, The Netherlands, Dept of Surgery and Liver research group[3], University of Birmingham, United Kingdom

14.10 Incidence and Management of Biliary Leakage after Partial Liver Resection (p. 46)
D. Erdogan[1], O.R.C. Busch[1], O.M. van Delden[2], E.A.J. Rauws[3], D.J. Gouma[1], T.M. van Gulik[1]. Depts of Surgery[1], Radiology[2] and of Gastroenterology and Hepatology[3], Academic Medical Center, University of Amsterdam, The Netherlands

14.20 Pancreas preserving total duodenectomy for patient with familial adenomatous polyposis of the duodenum: a comparison with pancreatoduodenectomy (p. 47)
S.M.M. de Castro[1], H.G. Smeenk[2], J.P. Rutten[3], H. van Goor[4], C.H.J. van Eijck[2], O.R.C. Busch[1], T.M. van Gulik[1], D.J. Gouma[1]. Depts of Surgery, Academic Medical Center[1], Amsterdam, Erasmus Medical Center[2], Rotterdam, University Hospital Maastricht[3], Maastricht, University Medical Center St. Radboud[4], Nijmegen, The Netherlands

Donderdag 16 maart 2006

14.30 Increased number of resections and more conservative management of patients with primary cystic neoplasms of the pancreas (p. 48)
S.M.M. de Castro[1], J.T. Houwert[1], O.R.C. Busch[1], T.M. van Gulik[1], H. Obertop[2], D.J. Gouma[1]. Academic Medical Center[1], Amsterdam and Erasmus Medical Center[2], Rotterdam, The Netherlands

14.40 Pancreaticoduodenectomy without preoperative radiological and histological diagnosis. Diagnostic strategy/management (p. 49)
N.A. van der Gaag[1], C.Y. Nio[2], M.I. van Berge Henegouwen[1], T.M. van Gulik[1], M.J. Bruno[3], O.R. Busch[1], E.A.J. Rauws[3], P. Fockens[3], D.J. Gouma[1]. Depts of Surgery[1], Radiology[2] and Gastroenterology[3], Academic Medical Center, Amsterdam, The Netherlands

14.50 Incidence of Focal Pancreatitis after pancreatoduodenectomy and the differentiation based on the clinical presentation and imaging. (p. 50)
L.C.F. de Nes[1], S.M.M. de Castro[1], B.W. Spanier[2], M.J. Bruno[2], O.R.C. Busch[1], S.S. Phoa[3], J.S. Laméris[3], T.M. van Gulik[1], D.J. Gouma[1]. Depts of Surgery[l], Gastroenterology[2] and Radiology[3], Academic Medical Center, Amsterdam, The Netherlands

15.00 Theepauze

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

15.30 Endoscopic and Surgical therapy is successful after complicated End to End Anastomosis in Bile Duct Injury patients (p. 51)
P.R. de Reuver[1], J.S Lameris[2], E.A. Rauws[3], O.R.C. Busch[1], T.M. van Gulik[1], D.J. Gouma[1]. Dept of Surgery[1], Radiology[2] and Gastroenterology[3], Academic Medical Center, Amsterdam, The Netherlands

15.40 Evaluation of available scoring systems to predict ongoing intra-abdominal infection in patients with secondary peritonitis and the need for relaparotomy. (p. 52)
O. van Ruler[1], J.B. Reitsma[2], E.A. Reuland[1], C.W. Mahler[1], D.J. Gouma[1], M.A. Boermeester[1], Dept. of Surgery[1], Dept. of Clinical Epidemiology and Biostatistics[2], Academic Medical Center, Amsterdam, The Netherlands

15.50 Intestinal permeability is associated with severity of disease in surgical ICU patients. (p. 53)
F. Hietbrink, M.G.H. Besselink, H. van Santvoort, M. de Smet, W. Renooij, L.M.A. Akkermans, L.P.H. Leenen. Dept of Surgery, University Medical Center Utrecht, The Netherlands

16.00 Non-elective colectomy in patients with fulminating colitis A systematic review of the literature. (p. 54)
P.H.E.Teeuwen, M.J.W. Stommel*, A.J.A. Bremers, R.P. Bleichrodt. *both authors contributed equally to this study Dept of Surgery, Radboud University Medical Centre, Nijmegen, The Netherlands*

16.10 Systematic review of short-term outcomes after laparoscopic ileocolic resection for Crohn's disease (p. 55)
S.W. Polle[1], J. Wind[1], D.Th. Ubbink[2], D.J. Gouma[1], W.A. Bemelman[1]. Depts of Surgery[1] and Clinical Epidemiology and Biostatistics[2], Academic Medical Center, Amsterdam, The Netherlands

16.20 Molecular characteristics of small bowel carcinomas vary with location (p. 56)
M. Berkhout[1], L.J.M. Mekenkamp[2], F.J.J.M. van de Molengraft[3], W.H.M. Peters[1], F.M. Nagengast[1], J.H.J.M. van Krieken[2], I.D. Nagtegaal[2]. Depts of Gastroenterology and Hepatology[1] and Pathology[2], Radboud University Nijmegen Medical Centre, Nijmegen, Dept of Pathology[3], Rijnstate Hospital, Arnhem, The Netherlands

Small bowel carcinomas; an immunohistochemical comparison of sporadic, Familial Adenomatous Polyposis and Celiac disease related tumors (p. 57)
M. Berkhout[1], L.J.M. Mekenkamp[2], F.J.J.M. van de Molengraft[3], W.H.M. Peters[1], F.M. Nagengast[1], J.H.J.M. van Krieken[2], I.D. Nagtegaal[2].Depts of Gastroenterology and Hepatology[1] and Pathology[2], Radboud University Nijmegen Medical Centre, Nijmegen, Dept of Pathology[3], Rijnstate Hospital, Arnhem ,The Netherlands

Bovenstaande abstracts worden als combinatievoordracht gepresenteerd door M. Berkhout.

Donderdag 16 maart 2006

16.30 Prevalence of adenomas and carcinomas in the ileal pouch in patients with familial adenomatous polyposis. (p. 58)
P. Friederich[1], E.*M.H. Mathus-Vliegen[4], G. Griffioen[2], F.M. Nagengast[1], H.F.A. Vasen[2,3]. Dept of Gastrointestinal and Liver Diseases, Radboud University Nijmegen Medical Center[1], Leiden University Medical Center[3], Academic Medical Centre; University of Amsterdam[4], Foundation for the Dectection of Hereditary Tumours[2], Leiden, The Netherlands*

16.40 Risk analyses for sigmoidoscopy as a screening tool based on the incidence of proximal colorectal carcinomas in a general hospital (p. 59)
S.A. Mulder[1,2], R.J.Th. Ouwendijk[1], M.E. van Leerdam[2], E.J. Kuipers[2]. Dept of Gastroenterology[1], Ikazia Hospital, Dept of Gastroenterology[2], Erasmus MC, Rotterdam, The Netherlands

16.50 Quality of life after Transanal Endoscopic Microsurgery and Total Mesorectal Excision in early rectal cancer (p. 60)
P.G. Doornebosch[1], R.A.E.M. Tollenaar[2], M.P. Gosselink[1], L.P. Stassen[3], W.R. Schouten[4], E.J.R. de Graaf[1]. Depts of Surgery, IJsselland Hospital[1], Capelle aan den IJssel, Leiden University Medical Center[2], Leiden, Reinier de Graaf Groep[3], Delft, Erasmus University Medical Center[4], Rotterdam, The Netherlands

17.00 Einde programma, congresborrel in expositiehal

Sectie Neurogastroenterologie en Motiliteit — Baroniezaal

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

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

13.00 The Diagnostic Value of the Proton Pump Inhibitor Test for Gastroesophageal Reflux Disease: A population-based study (p. 61)
M.C. Aanen[1], B.L.A.M. Weusten[2], M.E. Numans[3], N.J. de Wit[3], A. Baron[1], A.J.P.M. Smout[1]. Gastrointestinal Research Unit[1], University Medical Center, Utrecht, Dept of Gastroenterology[2], Sint Antonius Hospital, Nieuwegein, The Netherlands. Julius Center for Health Sciences and Primary Care[3], University Medical Center, Utrecht, The Netherlands

13.10 Characteristics of gastro-oesophageal reflux in symptomatic patients with and without excessive distal oesophageal acid exposure (p. 62)
A.J. Bredenoord[1], B.L.A.M. Weusten[1], R. Timmer[1], A.J.P.M. Smout[2]. Dept of Gastroenterology[1], St Antonius Hospital, Nieuwegein and Gastrointestinal Research Unit[2], University Medical Center, Utrecht, The Netherlands

13.20 Involvement of cannabinoid receptors in the triggering of TLESRs in healthy subjects (p. 63)
H. Beaumont[1], M. Ruth[2], J. Jensen[3], A. Lehmann[3], G. Boeckxstaens[1]. Dept of Gastroenterology and Hepatology[1], Academic Medical Centre, Amsterdam, The Netherlands, Dept of experimental Medicine[2], AstraZeneca R&D, Molndal, Sweden and Department of Gastrointestinal Biology, Integrative pharmacology[3], AstraZeneca R&D, Molndal, Sweden

13.30 Effect of distraction and attention on the frequency of belching in patients with aerophagia (p. 64)
A.J. Bredenoord[1], B.L.A.M. Weusten[1], R. Timmer[1], A.J.P.M. Smout[2]. Dept of Gastroenterology, St Antonius Hospital[1], Nieuwegein and Gastrointestinal Research Unit, University Medical Center[2], Utrecht, The Netherlands

13.40 The Manometric Common Cavity Phenomenon is an Unreliable Indicator of Gastroesophageal Reflux (p. 65)
M.C. Aanen[1], A. J. Bredenoord[2], M. Samsom[1], A.J.P.M. Smout[1]. Gastrointestinal Research Unit[1], University Medical Center, Utrecht, Dept of Gastroenterology[2], Sint Antonius Hospital, Nieuwegein, The Netherlands

13.50 Relationship between impaired drinking capacity and intragastric distribution in patients with functional dyspepsia. (p. 66)
B.D.J. van den Elzen[1], R.J. Bennink[2], B. Braak[1], G.E.E. Boeckxstaens[1]. Depts of Gastroenterology[1] and Nuclear medicine[2], Academic Medical Center Amsterdam, Amsterdam, The Netherlands

14.00 Patients with Gastroparesis Have a Decreased Expression of the 5-HT4(C) Splice Variant in the Duodenum (p. 67)
N. van Lelyveld[1], J. Ter Linde[1], M.E.I. Schipper[2], M. Samsom[1]. Dept of Gastroenterology[1] and Pathology[2], University Medical Centre Utrecht, Utrecht, The Netherlands

Donderdag 16 maart 2006

14.10 i.c.v. infusion of semapimod ameliorates postoperative ileus in mice. (p. 68)
F.O. The[1], W.J. de Jonge[1], J. van der Vliet[2], R.J. Bennink[1], R.M. Buijs[2], G.E. Boeckxstaens[1]. Academic Medical Center[1], Amsterdam and Netherlands Institute for Brain Research[2], Amsterdam, The Netherlands

14.20 Alpha-7 selective nicotinergic agonist ameliorates postoperative ileus by inhibiting activation of intestinal macrophages (p. 69)
W.J. de Jonge, F.O. The, E.P. van der Zanden, R.M. van den Wijngaard, G.E. Boeckxstaens. Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands

14.30 Non genomic transmission of visceral hypersensitivity across generations after maternal separation. (p. 70)
R.M. van den Wijngaard, O. Welting, P.H. Looijmans, W.J. de Jonge, G.E. Boeckxstaens. Academic Medical Center, Amsterdam, The Netherlands

14.40 Increased Visceroperception in Patients with Ulcerative Colitis in Remission is related to Mucosal Mast Cell Quantity (p. 71)
E.A. van Hoboken, R. Verhaaren, A.Y. Thijssen, P.P.J. van der Veek, H.W. Verspaget, A.A.M. Masclee, Dept of Gastroenterology-Hepatology, Leiden University Medical Center, Leiden, The Netherlands

14.50 Intestinal handling during abdominal surgery induces mast cell degranulation and intestinal inflammation in man (p. 72)
F.O. The[1], R.J. Bennink[1], W.M. Ankum[1], M.R. Buist[1], M.P.M. Burger[1], S. van der Heide[2], R.M. van den Wijngaard[1], W.J. de Jonge[1], G.E. Boeckxstaens[1]. Academic Medical Center[1], Amsterdam, University Medical Center[2], Groningen, The Netherlands

15.00 Theepauze, expositie

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

Voorzitter: C.H.C. Dejong

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

15.30 Is Cyst(e)ine an Essential Amino Acid in Borderline Preterm Infants?*(p 73)
M.A. Riedijk[1], R.T.H. van Beek[2], G. Voortman[3], J.B. van Goudoever[1]. Dept of Neonatology[1], and Mass Spectrometry Laboratory/Internal Medicine[3] Erasmus MC-Sophia Children's Hospital, Rotterdam and Dept of Pediatrics[2], Amphia Hospital, Breda, The Netherlands

15.40 The clinical effect of a new infant formula in term infants with constipation: a double-blind, randomized, cross-over trial * (p. 74)
M.E.J. Bongers[1], F. de Lorijn [1], J.B. Reitsma [2], M.I. Groeneweg [3], J.A.J.M. Taminiau [1], M.A. Benninga[1]. Dept of Pediatric Gastroenterology and Nutrition[1] and Dept of Biostatistics[2], Emma Children's Hospital, Academic Medical Center, Amsterdam, Dept of Pediatrics[3], St Clara Hospital, Rotterdam, The Netherlands

15.50 Effect of Body Position Changes on Postprandial Gastroesophageal Reflux and Gastric Emptying in the Premature Neonate * (p. 75)
M.P. van Wijk[1,4], M.A. Benninga[1], N. Rommel[2], J. Dent[3]. G.P. Davidson[4], T. Omari[4]. Dept of Paediatric Gastroenterology and Nutrition[1], Emma Children's Hospital, Amsterdam, The Netherlands. Catholic University of Leuven[2], Leuven, Belgium, Royal Adelaide Hospital[3] and Women's & Children's Hospital[4], Adelaide, SA, Australia

16.00 Gluten tolerance in coeliac disease patients * (p. 76)
G.D. Hopman[1], B.M.E. von Blomberg[2], E.M.C. Kooy-Winkelaar[1], J. Morreau[1], F. Koning[1], C.B.H.W. Lamers[1], M.L. Mearin[1]. Leiden University Medical Center[1], Leiden, Free University Medical Center[2], Amsterdam, The Netherlands

16.10 Cladribine therapy in refractory celiac disease with aberrant T-cells (p. 77)
M.S. Goerres[1], A. Al-toma[2], J.W.R. Meijer[1], B.M.E. von Blomberg[4], J.A.M. Kerckhaert[3], P.J. Wahab[3], C.J.J. Mulder[2]. Depts of Pathology[1] and Gastroenterology[3], Rijnstate Hospital, Arnhem, Depts of Gastroenterology[2], Clinical Pathology[4] and Microbiology[5] Free University Medical Center, Amsterdam, The Netherlands

Donderdag 16 maart 2006

16.20 Intestinal Fatty Acid Binding Protein: The role of the gut in the early phase of sepsis (p. 78)
J.P.M. Derikx[1], M. Poeze[1], A.A. van Bijnen[1], J.H. Zwaveling[2], W.A. Buurman[1], E. Heineman[1]. Depts of Surgery[1] and Intensive Care[2], University Hospital Maastricht/Maastricht University, Maastricht, The Netherlands

16.30 The clinical significance of plasma arginase-1 during liver surgery; effects of hepatocyte injury on arginase-1 release and plasma arginine levels in man. (p. 79)
M.C.G. van de Poll, S.J.P. Hanssen, M. Berbée, N.E.P. Deutz, W.A. Buurman, C.H.C. Dejong. Dept of Surgery, University Hospital Maastricht and Nutrition and Toxicology Research Institute Maastricht (NUTRIM), Maastricht University, The Netherlands

16.40 Decreased circulating arginine in ALF mice does not compromise whole body NO production (p. 80)
G.A.M. Ten Have[1], R. Jalan[2], N.E.P. Deutz[1]. Dept of Surgery[1], University Maastricht, The Netherlands, Institute of Hepatology[2], UCL, London, UK

16.50 Glutamine Is An Important Precursor For De Novo Synthesis Of Arginine In Man (p. 81)
G.C. Melis[1], M.C.G. van de Poll[2], P.G. Boelens[1], P.A.M. van Leeuwen[1], N.E.P. Deutz[2], C.H.C. Dejong[2]. Free University Medical Centre[1], Amsterdam and Maastricht University Hospital[2], Maastricht, The Netherlands

17.00 Einde programma in deze zaal.

** abstracts ingediend voor de Sectie Kindergastroenterologie*

Nederlandse Verenging voor Hepatologie **Parkzaal**

Voorzitters: B. van Hoek en J.P.H. Drenth

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

13.00 Significant liver damage in patients with bleeding disorders and chronic hepatitis C: non-invasive assessment of liver fibrosis using transient elastography (Fibroscan®) (p. 82)
D. Posthouwer[1], E.P. Mauser-Bunschoten[1], K. Fischer[2], K.J. van Erpecum[3], R.J. de Knegt[4]. Van Creveld Kliniek[1], Julius Center for Health Services and Primary Care[2], and Dept Gastroenterology[3], University Medical Center Utrecht, Dept Gastroenterology & Hepatology[4], Erasmus MC University Medical Center Rotterdam, The Netherlands

13.10 Liver injury in long-term Methotrexate treatment in psoriasis is relatively infrequent. (p. 83)
M.A.M. Berends[1], J. Snoek[2], P.C.M. van de Kerkhof[1], E.M.G.J. de Jong[1], M.G.H. van Oijen[2], J.P.H. Drenth[2]. Radboud University Nijmegen Medical Center, Depts of Dermatology[1] and Gastroenterology & Hepatology[2], Nijmegen, The Netherlands

13.20 Aberrant staining of hepatocystin in polycystic liver disease (p. 84)
E. Waanders[1], H.J. Croes[2], J.A. Fransen[2], J.B.M.J. Jansen[1], J.P.H. Drenth[1]. Dept of Gastroenterology and Hepatology[1], Radboud University Nijmegen Medical Center, Nijmegen, Dept of Cell Biology, Nijmegen Center for Molecular Life Sciences[2], Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

13.30 First in vitro comparison of two bioartificial liver support systems: MELS CellModule and AMC-BAL. (p. 85)
P.P.C. Poyck[1], G. Pless[2], R. Hoekstra[1,3], S. Roth[2], A.C.W.A. van Wijk[1], R. Schwartlander[2], T.M. van Gulik[1], I.M. Sauer[2], R.A.F.M. Chamuleau[4]. Dept Surgery (Surgical Laboratory)[1], Academic Medical Center Liver Center[3] and Dept Gastroenterology and Hepatology[4], Academic Medical Center, Amsterdam, The Netherlands; Dept Surgery[2], Campus Virchow Klinikum, Charité Universitätsmedizin Berlin, Germany

Donderdag 16 maart 2006

13.40 Endoscopic Treatment of Esophagogastric Variceal Bleeding in Patients with Non-cirrhotic Extrahepatic Portal Vein Thrombosis: A Long-term Follow-up Study. (p. 86)
V.M.C.W. Spaander[1], S. Darwish Murad[1], H.R. van Buuren[1], B.E. Hansen[2], E.J. Kuipers[1], H.L.A. Janssen[1]. Depts of gastroenterology and hepatology[1] and dept of biostatistics[2], Erasmus University Medical Centre, Rotterdam, The Netherlands

13.50 Does MELD Predict Survival in Budd-Chiari Syndrome? (p. 87)
S. Darwish Murad[1], R.W. Kim[2], P.S. Kamath[2], P.C. de Groen[2], H.L.A. Janssen[1]. Depts of Gastroenterology and Hepatology, Erasmus MC, University Medical Center Rotterdam[1], The Netherlands and Mayo Clinic College of Medicine[2], Rochester, MN, United States of America

14.00 Ursodeoxycholic acid exerts no beneficial effects in gallstone patients awaiting cholecystectomy: a randomized, double-blind, placebo-controlled trial. (p. 88)
N.G. Venneman[1], M.G.H. Besselink[1], Y.C.A. Keulemans[1], G.P. van Berge Henegouwen[1], M.A. Boermeester[2], I.A.M.J. Broeders[1], P.M.N.Y.H. Go[3], K.J. van Erpecum[1]. Gastrointestinal Research Unit and Depts of Gastroenterology and Surgery[1], University Medical Center Utrecht; Dept of Surgery[2], Academic Medical Center, Amsterdam; Dept of Surgery[3], St. Antonius Hospital, Nieuwegein, The Netherlands

14.10 Chronic renal failure after liver transplantation (p. 89)
S. van Laarhoven[1], A.P. van den Berg[2], E.B. Haagsma[2], M.J.H. Slooff[1], K.P. de Jong[1]. Depts of Hepato-Pancreato-Biliary Surgery & Liver Transplantation[1] and Hepatology[2], University Medical Center Groningen, The Netherlands

14.20 Inflammatory bowel disease after liver transplantation: risk factors for recurrence and de novo disease. (p. 90)
R.C. Verdonk[1,2], G. Dijkstra[1], E.B. Haagsma[1], V.K. Shostrom[2], A.P. van den Berg[1], J.H. Kleibeuker[1], A.N. Langnas[2], D.L. Sudan[2]. Dept of Gastro-enterology and Hepatology[1], University Medical Center Groningen, Groningen, the Netherlands. Dept of Surgery, Section of Transplant Surgery[2], University of Nebraska Medical Center, Omaha NE, United States of America

14.30 Hepatotoxicity of long-term and low-dose 6-thioguanine in IBD patients (p. 91)

N.K.H. de Boer[1], L.P.L. Gilissen[2], L.J.J. Derijks[3], G. den Hartog[4], B.D. Westerveld[5], L.G.J.B. Engels[6], A.A. van Bodegraven[1], E. Bloemena[7] and C.J.J. Mulder[1]. Free University Medical Center[1,7], Academic Hospital Maastricht[2], Maxima Medical Center[3], Rijnstate Hospital[4], Isala Clinics[5], Maasland Hospital[6], The Netherlands

Nodular regenerative hyperplasia and sinusoidal dilatation of the liver in a non-thiopurine using IBD-cohort (p. 92)

N.K.H. de Boer[1], H. Tuynman[2], E. Bloemena[3], J. Westerga[4], C.J.J. Mulder[1], M.A. Cuesta[5], S.G.M. Meuwissen[1], C.M.J. van Nieuwkerk[1], A.A. van Bodegraven[1]. Dept of Gastroenterology and Hepatology[1], Pathology[3] and Surgery[5], Free University Medical Center, Amsterdam, depts of Gastroenterology and Hepatology[2] and Pathology[4], Slotervaart Hospital, Amsterdam, The Netherlands

Bovenstaande abstracts worden als combinatievoordracht gepresenteerd door N.K.H. de Boer.

14.40 Assessment of the future remnant liver before partial liver resection: A comparison between liver volume and function measured by hepatobiliary scintigraphy. (p. 93)

W. de Graaf[1], R.J. Bennink[2], K.P. van Lienden[3], T.M. van Gulik[1]. Depts of Surgery/Surgical Laboratory[1], Nuclear Medicine[2] and Radiology[3], Academic Medical Center, University of Amsterdam, The Netherlands

14.50 Is the preferred treatment of hepatocellular adenoma conservative or surgical? (p. 94)

N.F.M. Kok[1], D.J. van der Windt[1], S.M. Hussain[2], P.E. Zondervan[3], I.P.J. Alwayn[1], R.A. de Man[4], J.N.M. IJzermans[1]. Dept of Surgery[1], Radiology[2], Pathology[3] and Hepato-gastro-enterology[4], Erasmus MC, Rotterdam, The Netherlands

15.00 Theepauze, expositie

Symposium: 'Interventions in Hepatology'

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

15.30 Endovasculaire interventies bij leverziekten
Prof. dr. J.S. Laméris, radioloog,
Academisch Medisch Centrum, Amsterdam

16.00 Endoscopische behandeling van Primair scleroserende cholangitis
Dr. E.A.J. Rauws, maag-darm-leverarts,
Academisch Medisch Centrum, Amsterdam

16.30 Leverbiopsieën en echografisch onderzoek van de lever
Dr. R.J. de Knegt, maag-darm-leverarts, Erasmus MC, Rotterdam

17.00 Endoscopic treatment of bleeding varices in the oesophagus and stomach
Prof. R. de Franchis, University of Milan,
Gastroenterology and GI Endoscopy Service Milan, Italy

17.30 Einde programma, congresborrel in de expositiehal

18.00 Diner Genderzaal

Presidential Selection - plenaire avondsessie **Diezezaal**

Voorzitter: J.B.M.J. Jansen

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

20.00 A Blinded, Randomized, Sham-Controlled Trial of Endoscopic Gastroplication for the Treatment of Gastro-Esophageal Reflux Disease (GERD) (p. 95)
M.P. Schwartz[1], H. Wellink[1], H.G. Gooszen[2], M. Samsom[1], A.J.P.M. Smout[1]. Depts of Gastroenterology[1] and Surgery[2], University Medical Center Utrecht, The Netherlands

One-year Follow-up after a Randomized, Sham-Controlled Trial of Endoscopic Gastroplication for the Treatment of Gastroesophageal Reflux Disease (GERD) (p. 96)
M.P. Schwartz[1], H. Wellink[1], H.G. Gooszen[2], M. Samsom[1], A.J.P.M. Smout[1]. Depts of Gastroenterology[1] and Surgery[2], University Medical Center Utrecht, Utrecht, The Netherlands

Bovenstaande abstracts worden als combinatievoordracht gepresenteerd door M.P. Schwartz

20.15 Bone Morphogenetic Protein (BMP)-4-mediated transformation of inflamed squamous esophageal mucosa into Barrett's Esophagus (p. 97)
J.W.P.M. van Baal[1]; F. Milano[1]; N.S. Buttar[2]; A.M. Rygiel[1]; F. de Kort[1]; J.J.G.H.M. Bergman[3]; K.K. Wang[2]; M.P. Peppelenbosch[4]; K.K. Krishnadath[3]. Laboratory of Experimental Internal Medicine[1], Academic Medical Center, Amsterdam, The Netherlands. Dept of Gastroenterology and Hepathology[2], Mayoclinic, Rochester, USA. Dept of Gastroenterology and Hepatology[3], Academic Medical Center, Amsterdam, The Netherlands. Dept of Cell Biology[4], University of Groningen, The Netherlands

20.30 Genotype-phenotype correlations as a guide in the management of familial adenomatous polyposis (p. 98)
M.H. Nieuwenhuis[1,2], E.M. Mathus-Vliegen, G. Griffioen, F.M. Agengast, C. Tops, W.R. Schouten, J.H. Kleibeuker, F. Slors, H.F.A. Vasen.
Netherlands Foundation Detection of Heretary Tumours[1] and Dept of Gastroenterology[2], Leiden University Medical Center, Leiden, The Netherlands

Donderdag 16 maart 2006

20.45 Sustained virological response leads to an improved clinical outcome in patients with hepatitis C and advanced fibrosis (p. 99)
B.J. Veldt[1], E.J. Heathcote[2], H. Wedemeyer[3], J. Reichen[4], W.P. Hofmann[5], S. Zeuzem[5], M.P. Manns[3], B.E. Hansen[1,6], S.W. Schalm[1], H.L.A. Janssen[1]. Erasmus MC University Medical Center, Depts of Gastroenterology & Hepatology[1] and Epidemiology & Biostatistics[6], Rotterdam, The Netherlands. Toronto Western Hospital[2], University Health Network, Toronto, Ontario, Canada. Dept of Gastroenterology, Hepatology and Endocrinology[3], Medizinische Hochschule Hannover, Hannover, Germany. Institute of Clinical Pharmacology[4], University of Berne, Berne, Switzerland. Universitätsklinikum des Saarlandes[5], Klinik für Innere Medizin II, Homburg /Saar, Germany

21.00 Ledenvergadering Nederlandse Vereniging voor Gastroenterologie in de **Diezezaal.**

22.00 Congresborrel in de Brabantzaal

Casuïstiek voor de clinicus — Brabantzaal

Voorzitter: W. Hameeteman

08.30 Casuïstische presentaties

09.20 Einde programma

Sectie Gastrointestinale Endoscopie — Brabantzaal

Voorzitter: W. Hameeteman

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

09.20 Endoscopic Tri-Modal Imaging (ETMI) for the Detection of Dysplastic Lesions in Barrett's Esophagus (p. 100)
W.L. Curvers[1,a], L.M. Wong Kee Song[1,b], K. Wang[1,b], C.J. Gostout[1,b], M.B. Wallace[1,c], H.C. Wolfsen[1,c], K. Ragunath[1,d], P. Fockens[1,a], F.J. ten Kate[2,a], K.K. Krishnadath[1,a], J.J. Bergman[1]. Dept of Gastroenterology & Hepatology[1], Dept of Pathology[2], Academic Medical Center[a], Amsterdam, The Netherlands, Mayo Clinic[b], Rochester, Jacksonville[c], USA, Queen's Medical Center[d], Nottingham, United Kingdom

09.30 Stepwise endoscopic resection of the whole Barrett's esophagus in patients with early neoplasia effectively removes all genetic alterations from the esophageal epithelium. (p. 101)
F.P. Peters[1], J.W.P.M. van Baal[2], A.M. Rygiel[2], W.L. Curvers[1], W.D. Rosmolen[1], P. Fockens[1], F.J.W. ten Kate[3], K.K. Krishnadath[1], J.J.G.H.M. Bergman[1]. Dept of Gastroenterology and Hepatology[1], Lab of Experimental Internal Medicine[2] and Dept of Pathology[3], Academic Medical Center, Amsterdam, The Netherlands

Vrijdag 17 maart 2006

09.40 Circumferential balloon-based radiofrequency ablation of Barrett's esophagus in patients with low-grade or high-grade dysplasia with and without a prior endoscopic resection using HALO360 Ablation System (p. 102)
J.J.G.H.M. Bergman[1], C.M.T. Sondermeijer[1], F.P. Peters[1], F.J. ten Kate[2], P.Fockens[1]. Depts of Gastroenterology and Hepatology[1] and Pathology[2], Academic Medical Center, Amsterdam, The Netherlands

09.50 Histological evaluation of resection specimens obtained at 244 endoscopic resections in Barrett's esophagus (p. 103)
K.P.M. Brakenhoff[1], F.P. Peters[1], W.L. Curvers[1], W.D. Rosmolen[1], F.J.W. ten Kate[2], K.K. Krishnadath[1], P. Fockens[1], J.J.G.H.M. Bergman[1]. Dept of Gastroenterology and Hepatology[1] and Pathology[2], Academic Medical Center, Amsterdam, The Netherlands

Endoscopic resection in esophagus and stomach is safe: a prospective analysis of 303 procedures (p. 104)
K.P.M. Brakenhoff[1], F.P. Peters[1], W.L. Curvers[1], W.D. Rosmolen[1], F.J.W. ten Kate[2], K.K. Krishnadath[1], P. Fockens[1], J.J.G.H.M. Bergman[1]. Depts of Gastroenterology and Hepatology[1] and Pathology[2], Academic Medical Center, Amsterdam, The Netherlands

Bovenstaande abstracts worden als combinatievoordracht gepresenteerd door K.P.M. Brakenhoff

10.00 Koffiepauze

10.30 The burden of upper gastrointestinal endoscopy in patients with Barrett's esophagus (p. 105)
M.E. Kruijshaar[1], P.D. Siersema[2], M. Kerkhof[2], E.W. Steyerberg[1], M.L. Essink-Bot[1]. Dept Public Health[1], Erasmus MC, University Medical Center Rotterdam, Rotterdam, Dept Gastroenterology and Hepatology[2], Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands

10.40 Large diameter stents are associated with a lower risk of recurrent dysphagia than small diameter stents (p. 106)
E.M.L. Verschuur, E.J. Kuipers, E.M. van Soest, P.D. Siersema. Dept of Gastroenterology & Hepatology, Erasmus MC/University Medical Center Rotterdam, The Netherlands

10.50 Effect of endoscopic gastroplication on acid and weakly acidic gastroesophageal reflux: a study using impedance monitoring (p. 107)
J.M. Conchillo, M.P. Schwartz, M. Selimah, A.J. Bredenoord, M. Samsom, A.J.P.M. Smout. Dept of Gastroenterology and Hepatology, University Medical Center, Utrecht, The Netherlands

11.00 Endoscopic pancreatic duct decompression in treating pancreatic leakage: a successful and safe method in selected patients (p. 108)
J.W. Poley[1], J. Heisterkamp[2], J. Dees[1], J. Haringsma[1], C.H.J. van Eijck[2], E.J. Kuipers[1], Depts of Gastroenterology and Hepatology[1] and Surgery[2], Erasmus MC, University Medical Center, Rotterdam, The Netherlands

11.10 Endoscopic ultrasound (EUS) guided transgastric drainage followed by endoscopic necrosectomy in patients with infected pancreatic necrosis: a retrospective cohort study (p. 109)
I.M. Schrover[1], B.L.A.M. Weusten[1], B. van Ramshorst[2], R.Timmer[1]. Dept of Gastroenterology[1] and Surgery[2], St Antonius Hospital, Nieuwegein, The Netherlands

11.20 Trends and forecasts for hospital admissions for acute and chronic pancreatitis in the Netherlands. (p. 110)
B.W.M. Spanier[1], M.G.W. Dijkgraaf[2], M.J. Bruno[1]. Depts of Gastro-enterology and Hepatology[1] and Clinical Epidemiology and Biostatistics[2], Academic Medical Center, Amsterdam, The Netherlands

11.30 High-resolution endoscopy and the additional value of chromoendoscopy in the evaluation of duodenal polyposis in FAP-patients. (p. 111)
E. Dekker[1], J. Dees[2], L. Mathus-Vliegen[1], J.W. Poley[2], J. Offerhaus[3], J. Bartelsman[1], E. Kuipers[2], P. Fockens[1]. Depts of Gastroenterology and Hepatology[1] and Pathology[3], Academic Medical Center Amsterdam and Dept of Gastroenterology and Hepatology[2], Erasmus Medical Center

11.40 Double Balloon Enteroscopy: Clinical outcome in 142 Overt- and occult gastrointestinal bleeding (OGIB) patients (p. 112)
H. Hekmat, G.D.N. Heine, A. Al-toma, C.J.J. Mulder, M.A.J.M. Jacobs. Dept of Gastroenterology, Free University Medical Center, Amsterdam, The Netherlands

11.50 einde programma

12.00 Lunchbuffet expositiehal

Nederlandse Vereniging voor Gastroenterologie **Baroniezaal**

Voorzitters: J.B.M.J. Jansen en A.J.P. van Tilburg

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

08.30 The tumor suppressor gene p53 as a predictor for development of esophageal cancer in patients with achalasia (p. 113)
I. Leeuwenburgh, A. Capello, M.M Gerrits, J.G Kusters, P.D. Siersema, E.J. Kuipers. Dept of Gastroenterology and Hepatology, Erasmus University Medical Center Rotterdam, The Netherlands

08.40 Clinical impact of gene polymorphisms of matrix metalloproteinases and their inhibitors in gastric cancer (p. 114)
F.J.G.M. Kubben[1], C.F.M. Sier[1], M.J.W. Meijer[1], M. van den Berg[1], J.J. van der Reijden[1], G. Griffioen[1], C.J.H. van de Velde[2], C.B.H.W. Lamers[1], H.W. Verspaget[1]. Depts of Gastroenterology-Hepatology[1] and Oncologic Surgery[2], Leiden University Medical Center, Leiden, The Netherlands

08.50 Quality of life and the presence of symptoms in treated achalasia patients, a cross-sectional study. (p. 115)
R. Frankhuisen[1], M.A. van Herwaarden[1], R. Heijkoop[1], A.J.P.M. Smout[1], A. Baron[1], J.R. Vermeijden[2], H.G. Gooszen[1], M. Samsom[1]. Gastrointestinal Research Unit, Depts of Gastroenterology and Surgery, University Medical Center Utrecht[1] and Meander Medical Center[2], Amersfoor

09.00 Measuring the severity of upper gastrointestinal complaints: does assessment correspond between general practitioner and patient? (p.116)
G.A.J. Fransen[1,2], M.J.R. Janssen[1], J.W.M. Muris[2], I. Mesters[3], A. Knottnerus[2]. Dept of Gastroenterology and Hepatology[1], Radboud University Nijmegen Medical Center, Nijmegen and Depts of General Practice [2] and Health Promotion & Health Education[3], Research Institute Caphri, Maastricht University, Maastricht, The Netherlands

09.10 Environmental risk factors for cancer development are not different between patients with esophageal and gastric cardia adenocarcinoma (p117)
L.M.M. Wolters, P.J.F. de Jonge, E.J. Kuipers, P.D. Siersema. Dept of Gastroenterology & Hepatology, Erasmus MC University Medical Center Rotterdam, The Netherlands

09.20 The COX-2 -765C -1195A haplotype predisposes for the development of esophageal adenocarcinoma (p. 118)
L.M.G. Moons[1,3], J.G. Kusters[1], A.M. Rygiel[2], Z.M.A. Groothuismink[1], W.A. Bode[3], H. Geldof[3], K.K. Krishnadath[2], J.G.H.M. Bergman[2], A.H.M. van Vliet[1], P.D. Siersema[1], E.J. Kuipers[1]. Depts of Gastroenterology, Erasmus MC[1], Rotterdam, Academic Medical Center Amsterdam[2] and IJsselland Hospital[3], Capelle a/d IJssel, The Netherlands

09.40 Comparison of conventional techniques and FLIP for the determination of OGJ characteristics in GERD patients pre and post laparoscopic Nissen fundoplication (p. 119)
H. Beaumont[1], B. McMahon[2], H. Gregersen[3], G. Boeckxstaens[1]. Dept of Gastroenterology[1], Academic Medical Centre, Amsterdam, The Netherlands, Dept of Medical Physics and Clinical Engineering, The Adelaide and Meath Hospital[2], Dublin, Ireland and Centre for Visceral Biomechanics and Pain, Dept of Gastroenterology[3], Aalborg Hospital, Aalborg, Denmark

09.50 Characterisation of Intraluminal Impedance Patterns Associated with Gas Reflux (Belching) in Healthy Volunteers * (p. 120)
M.P. van Wijk[1,4], D. Sifrim[2], M.A. Benninga[1], N. Rommel[2], G.P. Davidson[3], T. Omari[3]. Dept of Paediatric Gastroenterology and Nutrition[1], Emma Children's Hospital, Amsterdam, The Netherlands, Catholic University of Leuven[2], Leuven, Belgium. Women's & Children's hospital[3], North Adelaide, SA, Australia

10.00 Koffiepauze, expositie

Voorzitters: P.D. Siersema en B.G. Taal

10.30 Gene therapy in experimental models of esophageal carcinoma (p. 121)
(Final Report Maag Lever Darm Stichting projectno. WS 99-70)
W.A. Marsman, J.G. Wesseling, C.J. Buskens, J.J.B. van Lanschot and P.J. Bosma. Dept of Gastroenterology, Academic Medical Center Amsterdam, The Netherlands

10.40 Seven-day therapy with esomeprazole, amoxicillin and levofloxacin is very effective for H.pylori eradication (p. 122)
W.A. de Boer, M.E. Ouwehand, A.H. Vos, I.A.M. Gisbertz, M.J.R. Janssen. Dept of Gastroenterology, Bernhoven Hospital, Oss, The Netherlands

Vrijdag 17 maart 2006

10.50 Seroprevalence of Helicobacter pylori in two asymptomatic Dutch populations (p. 123)
A.J. van Vuuren[1], R.A. de Man[1], H.F. van Driel[3], M. Ouwendijk[1], J. G. Kusters[1], E.J. Kuipers[1], J.H. Richardus[2], P.D. Siersema[1], M. van Blankensteins[1]. Depts of Gastroenterology & Hepatology[1] and Public Health[2] , Erasmus MC, University Medical Center, Municipal Health Service[3], Rotterdam, The Netherlands

11.00 Depot octreotide therapy in dumping syndrome: long term follow up (p. 124)
P. Didden, C. Penning, A.A.M. Masclee. Dept of Gastroenterology-Hepatology, Leiden University Medical Center, Leiden, The Netherlands

11.10 Follow up of patients with carcinoid tumors: Combination of Chromogranin A and NT-proBNP. (p. 125)
J.M.G. Bonfrer[1], C.M. Korse[1], B.G. Taal[2]. Depts of Clinical Chemistry[1] and Medical Oncology[2], The Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands

11.20 Abnormalities of the enteric nervous system, smooth muscle and interstitial cells of Cajal in children with colonic motility disorders * (p. 126)
M.M. van den Berg[1], H.M. Mousa[1], C. Di Lorenzo[1], M.A. Benninga[2], G.E.E. Boeckxstaens[3], M. Luquette[4]. Depts of Pediatric Gastroenterology[1] and Pathology[4], Children's Hospital of Columbus, Columbus, Ohio, USA, Dept of Pediatric Gastroenterology, Emma Children's Hospital[2] Academic Medical Center, Amsterdam, Dept of Gastroenterology[3], Academic Medical Center, Amsterdam, The Netherlands

11.30 Clinical spectrum and survival in patients who presented with a Neuroendocrine tumours (NET) from 1995-2004. (p. 127)
B.G. Taal[1,2], M.E. Smits[2], J. Bonfrer[3], T.Korse[3] Depts of Medical Oncology[1], Gastroenterology[2] and Clinical Chemistry[3], Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands

11.40 Autologous Haematopoietic Stem Cell Transplantation in four Refractory Coeliacs with aberrant T-cells (p. 128)
A. Al-toma[1], O. Visser2, H.M. van Roessel[2], B.M.E. von Blomberg[3], P.E.T Scholten[3], G.J. Ossenkoppele[2], P.C. Huijgens[2], C.J.J. Mulder[1]. Dept of Gastroenterology[1] Haematology[2], Clinical Pathology[3], Free University Medical Center, Amsterdam, The Netherlands

11.50 In-vitro cytotoxicity of bile acids in small intestine and colon cell lines with or without UDCA. (p. 129)
C. Graven, H. Schaap-Roelofs, M.G.H. van Oijen, W.H.M. Peters, F.M. Nagengast, J.B.M.J. Jansen. Dept of Gastroenterology and Hepatology, University Medical Center, St Radboud, Nijmegen, The Netherlands

12.00 Lunchbuffet expositiehal

Sectie Experimentele Gastroenterologie — Parkzaal

Voorzitter: E.H.H.M. Rings en A.H.M. van Vliet

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

08.30 Effect of Aspirin on the Wnt/β-catenin Pathway is Mediated via Protein Phosphatase 2A (p. 130)
C.L. Bos[1,2], L. Kodach[3], G.R. van den Brink[4], S.H. Diks[5], M.M. van Santen[3], D.J. Richel[2], M.P. Peppelenbosch[5], J.C.H. Hardwick[4] From the [1]Lab of Experimental Oncology and Radiobiology, [2]Dept of Oncology, [3]Laboratory of Experimental Internal Medicine, [4]Dept of Gastroenterology, University of Amsterdam, the [5]Dept of Cell Biology, University of Groningen, The Netherlands.

08.40 Fur mediates iron-responsive repression of urease expression in Helicobacter hepaticus (p. 131)
C. Belzer, B.A.M. van Schendel, E.J. Kuipers, J.G. Kusters, A.H.M. van Vliet. Dept of Gastroenterology and Hepatology, Erasmus MC-University Medical Center, Rotterdam, The Netherlands

08.50 Adoptive transfer of non-transgenic mesenteric lymph node cells induces colitis in athymic hla-b27 transgenic nude rats (p. 132)
F. Hoentjen[1,2], S.L. Tonkonogy[3], B. Liu[1], R.B. Sartor[1], J.D. Taurog[4], L.A. Dieleman[5]. Dept of Gastroenterology[1], University of North Carolina, Chapel Hill, USA; Free University Medical Center[2], Amsterdam, The Netherlands; North Carolina State University[3], Raleigh, USA; University of Texas Southwestern Medical Center[4], Dallas, USA; University of Alberta[5], Edmonton, Canada

Vrijdag 17 maart 2006

09.00 KRAS and BRAF mutations are rare in early adenomas from patients with familial adenomatous polyposis and MYH-associated polyposis. (p. 133)
M.E. van Leerdam[1], J. Cordoso[2], L. Molenaar[2], J. Boer[3], H. Morreau[4], G. Moslein[5], J. Sampson[6], E. Kuipers[1], R. Fodde[2]. Depts of Gastroenterology and Hepatology[1] and Pathology JNI[2], Erasmus Medical Center, Rotterdam, Center for Human & Clinical Genetics[3] and Dept of Pathology[4], Leiden University MC The Netherlands, Dept of Surgery[5] Heinrich Heine University, Dusseldorf, Germany

09.10 Association of Y chromosome haplotypes with Barrett's esophagus and Esophageal Adenocarcinoma in the Dutch Caucasian population. (p. 134)
A.M. Rygiel, S. Repping[3], L.M.G. Moons[5], J.G Kusters[5], S. Ouburg[6], F. Milano[1], J.W.P.M van Baal[1], S.A Morre[6], C. Mulder[6], J.G.H.M Bergman[2], M.P Peppelenbosch[4], P.Siersema[5], J.M Hoovers[3], K.K Krishnadath[2]. Depts of Experimental Internal Medicine[1], Gastroenterology and Hepatology[2] and Center for Reproductive Medicine[3], Aacademic Medical Center, Amsterdam, Dept of Cell Biology[4], University of Groningen, Dept of Gastro-enterology and Hepatology[5],Erasmus MC UM, The Netherlands

09.20 Indomethacin enhances bile salt detergent activity: relevance for NSAIDs-induced gastrointestinal mucosal injury. (p. 135)
M. Petruzzelli[2], A. Moschetta[2], W. Renooij[1], M.B.M. de Smet[1], G. Palasciano[2], P. Portincasa[2], K.J. van Erpecum[1]. Gastrointestinal Research Unit, Depts of Gastroenterology and Surgery[1], University Medical Center Utrecht, Utrecht, The Netherlands, and Section of Internal Medicine, Dept of Internal and Public Medicine[2], University of Bari, Italy

09.30 Helicobacter pylori inhibits proliferation but not activation of T-cells. (p. 136)
C.M. Dierikx, B.M. Bosma, E.J. Kuipers, J.G. Kusters, J. Kwekkeboom. Dept of Gastroenterology and Hepatology, Erasmus MC, Rotterdam, The Netherlands

09.40 The role of the p110δ PI3-kinase isoform in inflammatory bowel disease (p. 137)
K. Kok[1], W.P. Pearce[2], M.P. Peppelenbosch[3], B. Vanhaesebroeck[2], D.W. Hommes[1]. Experimental Internal Medicine[1], Academic Medical Center, Amsterdam, The Netherlands, Ludwig Institute for Cancer Research[2], London, United Kingdom, Cell Biology[3], University of Groningen, Groningen, The Netherlands

09.50 Altered Bone Morphogenetic Protein signaling in the Helicobacter pylori infected stomach (p. 138)
S.A. Bleuming,[1], L.L. Kodach[1], M.J. Garcia Leon,[1], D. Richel,[2;] M.P. Peppelenbosch,[1], P.H. Reitsma,[1], J.C. Hardwick,[1], G.R. van den Brink[1] Depts of Experimental Internal Medicine[1] and Oncology,[2] Academic Medical Center, Amsterdam, The Netherlands

10.00 Koffiepauze

Sectie Experimentele Gastroenterologie **Parkzaal**

Voorzitter: E.A.F. van Tol en H.W. Verspaget

10.30 **International Teaching Session**
"Intestinal Ecology and Disease: the Interplay between Bacteria, Genes and Innate Immunity."

Microbial Ecology in Health and Gastrointestinal Disease
Prof. Tore Midtvedt, Microbiology and Tumour Biology Center, Karolinska Institute, Stockholm, Sweden.

Functional Interplay between TLR and NOD in IBD: Genes-Bacteria-Probiotics
Prof. Subrata Ghosh, Gastroenterology-Division of Medicine, Imperial College London, Hammersmith Hospital, United Kingdom.

12.00 Lunchbuffet expositiehal

Nederlandse Vereniging voor Gastroenterologie **Brabantzaal**

Voorzitter: J.H. Kleibeuker

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

13.30 Decreased cytotoxicity of bile after ursochol intervention in patients with familial adenomatous polyposis (FAP): a pilot study. (p. 139)
M. Berkhout[1], H.M.J. Roelofs[1], P. Friederich[1], A. van Schaik[1], Brigitte Marian[2], J.H.J.M. van Krieken[3], W.H.M. Peters[1], F.M. Nagengast[1]. Depts of Gastroenterology and Hepatology[1] and Pathology[3], Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands and Institute of Cancer Research[2], Medical University Vienna, Vienna, Austria

13.40 Direct access colonoscopy for general practitioners in the Netherlands is feasible and has a high diagnostic yield. (p. 140)
B.A. van Balkom, J.G. Goedhard, M.A. de Bievre, C.M. Bakker, C.Th.B.M. van Deursen, J. Rijken, P.J. van der Schaar, Atrium Medisch Centrum Heerlen, The Netherlands

13.50 A nationwide survey evaluating adherence to guidelines for follow-up after polypectomy or treatment for colorectal cancer (p. 141)
S.A. Mulder[1,2], R.J.Th. Ouwendijk[1], M.E. van Leerdam[2], E.J. Kuipers[2]. Dept of Gastroenterology[1], Ikazia Hospital, Zwolle and Dept of Gastro-enterology[2], Erasmus MC, Rotterdam, The Netherlands

14.00 Tumor M2-PK and immunochemical FOBT: screening for colorectal cancer (p. 142)
S.A. Mulder[1,2], M.E. van Leerdam[2], R.J.Th. Ouwendijk[1], A.J. van Vuuren[2], J. Francke[2], E.J. Kuipers[2]. Dept of Gastroenterology[1], Ikazia Hospital, Zwolle and Dept of Gastroenterology[2], Erasmus MC, Rotterdam, The Netherlands

14.10 Risk of colorectal cancer in Juvenile Polyposis (p. 143)
L.A.A. Brosens[1,2], A.C. Tersmette[2], L.M. Hylind[1], C. Iacobuzio-Donahue[1], K.E. Romans[1], J. Axilbund[1], A. van Hattem[2], G.J.A. Offerhaus[2], F.M. Giardiello[1]. Dept of Medicine, Division of Gastroenterology[1], The Johns Hopkins University School of Medicine, Baltimore, MD, USA, and Dept of Pathology[2], Academic Medical Center, Amsterdam, The Netherlands

14.20 The use of genetic testing in Hereditary Non-Polyposis Colorectal Cancer families. (p. 144)

D. Ramsoekh[1], A. Wagner[2], M.E. van Leerdam[1], D. Dooijes[2], C. Tops[3], H. Meijers-Heijboer[2], E.J. Kuipers[1]. Depts of Gastroenterology[1] and Human and Clinical Genetics[2], Erasmus Medical Center, Rotterdam and Dept of Human and Clinical Genetics[3], Leiden University Medical Center, Leiden, The Netherlands

14.30 Comparison of outcome of colonoscopic surveillance in HNPCC and ulcerative colitis (p. 145)

A.M.J. Langers[1], A.E. de Jong[1], C.B.H.W. Lamers[1], H.F.A. Vasen[1,2], R.A. van Hogezand[1]. Dept of Gastroenterology[1], Leiden University Medical Center and HNPCC Registry[2], Leiden, The Netherlands

14.40 Array-based genetic evaluation of adenocarcinomas and dysplastic lesions (DALM) in ulcerative colitis (p. 146)

J.M. van Dieren[1] , J.C. Wink[2] , K.J. Vissers[2] , R. van Marion[2] , W.R. Schouten[3] , H.J. Tanke[4] , K. Szuhai[4], E.J. Kuipers[1], C.J. van der Woude[1] and H. van Dekken[2]. Depts of Gastroenterology & Hepatology[1], Pathology[2], Surgery[3] and Lab of Cytochemistry and Cytometry, Dept of Molecula[4], Erasmus Medical Center Rotterdam The Netherlands

14.50 Relevance of small gallbladder stones, good gallbladder motility and fast crystallization in the pathogenesis of acute biliary pancreatitis, and efficacy of UDCA on biliary colics and complications in sympto-matic gallstone patients awaiting cholecystectomy. (p. 147)

(Final report Maag Lever Darm Stichting projectno. WS 00-08)

[1]N.G. Venneman, [1]W. Renooij, [2]J. F. Rehfeld, [1]G.P. van Berge Henegouwen, [3]P.M.N.Y.H. Go, [1]I.A.M.J. Broeders, [1]M.G.H. Besselink, [1]Y.C.A. Keulemans, [4]M.A. Boermeester, [1]K.J. van Erpecum. [1]Gastrointestinal Research Unit, Depts. of Gastroenterology and Surgery, University Medical Center Utrecht, The Netherlands; [2]Dept. of Clinical Biochemistry, Rigshospitalet, Copenhagen, Denmark; [3]Dept. of Surgery, St. Antonius Hospital, Nieuwegein, The Netherlands. [2]Dept. of Surgery, Academic Medical Centre, Amsterdam, The Netherlands.

15.00 Theepauze, expositie

Nederlandse Vereniging voor Gastroenterologie **Baroniezaal**

Voorzitter: B. Oldenburg

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

13.30 Identification and characterization of proteins involved in intestinal cholesterol absorption (p. 148)
(final report Maag Lever Darm Stichting projectno. WS 00-46)
F.R. Frijters, F.G. Schaap, A. Kosters, A.K. Groen. AMC Liver Center, Academic Medical Center, Amsterdam, The Netherlands

13.40 MR Enteroclysis in Celiac disease, Refractory Celiac disease and Enteropathy associated T-cell lymphoma (p. 149)
M.P.J.H. Mallant[1], G.M. Kater[1], A. Al Toma[2], J.H.T.M. van Waesberghe[1], C.J.J. Mulder[2]. Dept of Radiology[1] and Gastro-enterology[2], Free University Medical Center Amsterdam, The Netherlands

13.50 Tacrolimus enema treatment for left-sided colitis: a safety study (p. 150)
J.M. van Dieren[1], E.J. Kuipers[1], E.E.S Nieuwenhuis[2], C.J. van der Woude[1]. Dept of Gastroenterology & Hepatology[1], Erasmus MC, University Medical Center Rotterdam, Lab of Pediatrics, division of Gastroenterology & Nutrition[2], Erasmus MC, University Medical Center Rotterdam, The Netherlands

14.00 Azathioprine maintains first remission in newly diagnosed pediatric Crohn's disease * (p. 151)
G.J. Jaspers[1], H.J. Verkade[1], J.C. Escher[2], L. de Ridder[3], J.A.J.M. Taminiau[3], E.H.H.M. Rings[1]. Depts of Pediatrics, University Medical Center Groningen[1], Erasmus Medical Center Rotterdam[2], Academic Medical Center Amsterdam[3], The Netherlands

14.10 Regional differences of several bacterial species in the non-diseased human colon (p. 152)
H. Akol[1], C.M. Gundy[2], M.J.E. Vandenbroucke-Grauls[3], C.J.J. Mulder[1], P.H.M. Savelkoul[3], A.A. van Bodegraven[1]. Dept of Gastroenterology and Hepatology[1] , Dept of Clinical Epidemiology and Biostatistics[2], Dept of Medical Microbiology & Infection Control[3], Free University Medical Center, Amsterdam, The Netherlands

14.20 The role of colonoscopic biopsy in distinguishing Crohn's disease and intestinal tuberculosis (p. 153)
Ph.W. Friederich[1], R. Kirsch[2]. Depts of Gastroenterology[1] and Anatomical Pathology[2], Faculty of Health Sciences, University of Cape Town, South Africa

14.30 Adherence to surveillance guidelines for dysplasia and colorectal carcinoma in ulcerative and Crohn's colitis patients in the Netherlands (p. 154)
A. van Rijn[1,2], M. Samsom[2], P. Fockens [1], B. Oldenburg[2]. Dept of Gastroenterology and Hepatology[1], Academic Medical Center, Amsterdam, Dept of Gastroenterology[2], University Medical Center Utrecht, Utrecht, The Netherlands

14.40 First European database of pediatric inflammatory bowel disease (IBD) * (p. 155)
J. van der Kooy[1], J.C. Escher[1]. Erasmus MC-Sophia Children's Hospital[1], Rotterdam, The Netherlands and the ESPGHAN pediatric IBD (Porto) study group

14.50 Can three-dimensional endoanal ultrasonography detect external anal sphincter atrophy? A comparison with endoanal magnetic resonance imaging (p. 156)
R.L. West[1], S. Dwarkasing[2], J.W. Briel[3], B.E. Hansen[1], S.M. Hussain[2], W.R. Schouten[3], E.J. Kuipers[1]. Depts of Gastroenterology and Hepatology[1], Radiology[2], Surgery[3], Erasmus MC / University Medical Centre Rotterdam, The Netherlands

15.00 Theepauze, einde programma

* *abstracts ingediend voor de Sectie Kindergastroenterologie*

Sectie Experimentele Gastroenterologie — Parkzaal

Voorzitters: J.G. Kusters en M. Peppelenbosch

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

13.30 Immune stimulating effects of β-glucan on enterocytes in vitro: a possible role for dectin-1 (p. 157)
J.J. Volman[1], J.D. Ramakers[1], W.A. Buurman[2], R.P. Mensink[1], J. Plat[1]. Dept of Human Biology[1] and General Surgery[2], Nutrition and Toxicology Research Institute Maastricht, Maastricht University, The Netherlands

13.40 Glucocorticoids inhibit T cell receptor signaling via Lck and Fyn; a new immunosuppressive mechanism for an old drug (p. 158)
M. Löwenberg[1], J. Bilderbeek[1], A. Verhaar[1], F. Buttgereit[2], M. Peppelenbosch[3], S. van Deventer[1], D.W. Hommes[1]. Dept of Gastroenterology and Hepatology[1], Academic Medical Center, Amsterdam, The Netherlands, Charite University Hospital[2], Berlin, Germany, Dept of Cell Biology and Histology[3], University of Groningen, The Netherlands

13.50 Villous atrophy in celiac disease: uncovering the patho-mechanisms by immunohistochemistry and gene-expression studies (p. 159)
E. van Oort[1], E. Strengman[1], B. Diosdado[1], M.C. Wapenaar[1], J.W.R. Meijer[2], J.G.A. Offerhaus[3], C. Wijmenga[1]. DBG depts of Medical Genetics[1], University Medical Center Utrecht, Depts of Pathology, Rijnstate Hospital[2], Arnhem and Academic Medical Center Amsterdam[2], The Netherlands

14.00 The systemic cytokine response during experimental acute pancreatitis: impact of enteral probiotics (p. 160)
L.P. van Minnen[1], H.M. Timmerman[1,3], W. de Jager[3], S.R. Konstantinov[5], F. Lutgendorff[1], A. Verheem[1], W. Harmsen[2], M.R.Visser[2], H. Smidt[5], H.G. Gooszen[1], L.M.A. Akkermans[1], G.T. Rijkers[3,4]. Gastrointestinal Research Unit, Depts of Gastroenterology an Surgery[1], Dept of Microbiology[2], and Dept of Paediatric Immunology[3], University Medical Center, Utrecht, Dept of Medical Microbiology and Immunology[4], St. Antonius Hospital, Nieuwegein, Lab of Microbiology, Agrotechnology and Food Sciences Group[5], Wageningen University, The Netherlands

14.10 C-reactive protein and natural IgM antibodies are activators of complement in a rat model of intestinal ischemia and reperfusion (p. 161)
A.K. van Vliet[1], N. Diaz-Padilla[2], I.G. Schoots[1], M.A. Maas[1], E.E. Posno-Peltenburg[1], A. de Vries[1], H.W.N. Niessen[3], C.E. Hack[2], T.M. van Gulik[1]. Dept of Surgery (Surgical laboratory)[1], AMC,, University of Amsterdam, Amsterdam, Dept of Immunopathology, Sanquin Research, and laboratory of Experimental and Clinical Immunology[2], Amsterdam, Dept of Pathology[3], Free University Medical Center, Amsterdam, The Netherlands

14.20 Comparison of kinase profiles in Barrett's esophagus, normal squamous esophagus and normal gastric cardia proves that Barrett's esophagus has a high glycolytic activity (p. 162)
J.W.P.M. van Baal[1,2], S.H. Diks[1], A.M. Rygiel[2], F. Milano[2], J.J.G.H.M. Bergman[3], R.J.H. Wanders[4], M.P. Peppelenbosch[1], K.K. Krishnadath[3] · Dept of Cell Biology[1], University of Groningen, Lab of Experimental Internal Medicine[2], Dept of Gastroenterology and Hepatology[3], Lab for Genetic Metabolic Diseases[4], Academic Medical Center, Amsterdam

14.30 Regulation and role of the two Helicobacter mustelae TonB orthologs in iron acquisition (p. 163) *J. Stoof, J.G. Kusters, E.J. Kuipers, A.H.M. van Vliet. Dept of Gastroenterology and Hepatology, Erasmus MC, Rotterdam*

14.40 Impaired immune recognition of M. tuberculosis and M. paratuberculosis in Crohn patients homozygous for the NOD2 3020insC mutation (p. 164)
G. Ferwerda[1,2], D.J. de Jong[3], R. van Crevel[1,2], T.H.M. Ottenhoff[4], J.W.M. van der Meer[1,2], B.J. Kullberg[1,2], and M.G. Netea[1,2]. Dept of Internal Medicine[1] and Radboud University Nijmegen for Infectious Diseases[2], Dept of Gastroenterology[3], University Medical Center St. Radboud, Nijmegen, Dept of Immunohematology and Blood Transfusion[4], Leiden University Medical Center, The Netherlands

14.50 Bone Morphogenetic Protein (BMP) signaling regulates fundic gland homeostasis and suppresses tumorigenesis at gastric epithelial transition zones in mice (p. 165)
S.A. Bleuming[1]; X.C. He[3], L.L. Kodach[1], F.J. ten Kate[2], G.J. Offerhaus[2], S.J.H. van Deventer[1], J.C. Hardwick[1], M.P. Peppelenbosch[1], L. Li[3], G.R. van den Brink[1]. Depts of Experimental Internal Medicine[1] and Pathology, Academic Medical Center[2], Amsterdam, The Netherlands; Stowers Institute for Medical Research[3], Kansas City, USA

15.00 Theepauze, einde programma

Vrijdag 17 maart 2006

Sectie Endoscopie Assistenten en Verpleegkundigen **Diezezaal**

ochtendprogramma

10.00 – 10.30 uur	*Ontvangst, koffie*
10.30 – 11.50 uur	Achalasie Dhr. Dr. P. Scholten, MDL-arts, Lucas Andreas Ziekenhuis, Amsterdam
10.50 – 11.10 uur	Endoscopy in the future Dhr. Prof. J.F.W.M. Bartelsman, MDL-arts Academisch Medisch Centrum, Amsterdam
11.10 – 11.30 uur	Voorlichting betreffende fusie lidorganisaties van de Algemene Vereniging Verpleegkundigen en Verzorgenden Dhr. B. Vogel, AVVV, Utrecht
11.30 – 12.00 uur	**Ledenvergadering SEVA**
12.30 – 13.30 uur	*Lunchbuffet in de expositiehal*

middagprogramma

13.30 – 14.00 uur	Kwaliteitbeleid door middel van vaardigheidskaarten Mevr. A. Joossen, endoscopieverpleegkundige Oosterscheldeziekenhuis, Goes
14.00 – 14.30 uur	Nieuwe ontwikkelingen in de behandeling van IBD Dr. A.A. van Bodegraven, MDL-arts VU medisch centrum, Amsterdam
14.30 – 14.50 uur	Cortrex, nieuwe manier van plaatsing duodenumsonde Mevr. A. Duflou, endoscopieverpleegkundige Academisch Medisch Centrum, Amsterdam
14.50 uur	*Koffie/thee, einde programma*

Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the oesophagus: five year survival of a randomized clinical trial

J.M.T. Omloo[1], S.M. Lagarde[1], J.B.F. Hulscher[1], J.B. Reitsma[2], P. Fockens[3], H. van Dekken[4], F.J.W. ten Kate[5], H. Obertop[6], H.W. Tilanus[6], J.J.B. van Lanschot[1], Depts of Surgery[1], Clinical Epidemiology and Biostatistics[2], Gastroenterology[3] and Pathology[5], Academic Medical Centre, Amsterdam and Depts of Surgery[6] and Pathology[4] at the Erasmus Medical Centre, Rotterdam, The Netherlands

Introduction: The incidence of adenocarcinoma of the oesophagus is rapidly rising. It is an aggressive disease with early lymphatic and haematogenous dissemination. Surgery is the best curative treatment option. However, much controversy concerning the best surgical approach exists. An extended transthoracic resection has higher morbidity but possibly improved long-term survival, whereas a limited transhiatal resection minimizes surgical trauma.Methods: Between April 1994 and February 2000 a total of 220 patients with adenocarcinoma of the distal oesophagus (type I) or gastric cardia involving the distal oesophagus (type II) were randomly assigned to limited transhiatal oesophagectomy or to transthoracic oesophagectomy with extended en bloc lymphadenectomy. Patients with peroperatively irresectable cancer were excluded from this analysis (n=15). A total of 95 patients underwent transhiatal esophagectomy and 110 patients underwent transthoracic esophagectomy. Follow-up was completed in all patients.Results: After a minimal potential follow-up of five years a total of 133 patients (65%) had died. After transhiatal and transthoracic resection five-year survival was 34% and 36% respectively (p=0.69, per protocol analysis). In a subgroup analysis, where patients were divided by localisation of the primary tumour according to the resection specimen, no survival benefit was seen between surgical approaches in 115 patients with a tumour arising from the gastric cardia or at the gastro-oesophageal junction (type II; p=0.52). However, 90 patients with oesophageal cancer (type I) had 14% five-year survival benefit if operated via the transthoracic approach (37% compared to 51%, p=0.186). Conclusion: Extended transthoracic oesophagectomy for type I oesophageal adenocarcinoma shows an onoing trend towards better five-year survival.

Analysis of gene expression discovers pathways associated with hematogenous metastasis in patients with adenocarcinoma of the esophagus

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Introduction:The incidence of adenocarcinoma of the esophagus is rapidly rising. It is an aggressive disease with early hematogenous dissemination. The molecular analysis of esophageal cancer has mainly focused on the prognostic significance of alterations in single candidate genes. However, with use of microarrays, global gene expression profiling monitors changes in expression of individual cancer tissues of tens of thousands of genes. Extracting biological insight from these data remains a challenge. Gene Set Enrichment Analysis (GSEA) focuses on groups of genes that share common biological pathways, chromosomal location or regulation. The aim of this study was to identify gene sets that are associated with hematogenous dissemination in patients with adeno-carcinoma of the esophagus. Methods: From a tissue bank of consecutive patients operated on with curative intent two groups were selected. Patients who developed hematogenous dissemination (N=33) were compared with patients who had no signs of recurrence during at least three years of follow up (N=44). Whole genome microarrays containing 44.000 probes were used to evaluate the 77 esophageal cancer specimens. After quality control and normalisation, GSEA was applied to the microarray data using 1325 biologically defined gene sets and 100 permutation tests. Results: Five of the ten top-ranked gene sets that were significantly associated with hematogenous dissemination were related with the integrin signaling pathway which is associated with malignant progression by promoting tumor cell motility and invasion. Analysis of gene expression data according to chromosome location revealed several loci, most prominently 3p24. This locus encompasses 23 known genes and is also an important locus in prostate cancer. Conclusions: Pathway analysis reveals mechanisms that underlie hematogenous dissemination in patients with adenocarcinoma of the esophagus and offers novel strategies for investigation.

Surgical reintervention after antireflux surgery for gastro-esophageal reflux disease; a prospective cohort study in 130 patients

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Surgical reintervention after antireflux surgery for gastro-esophageal reflux disease (GERD) is required in 3-6% of patients. The subjective outcome after these reinterventions has been reported in several studies, but objective results after these reoperations are hardly published. The purpose of this study was to assess the symptomatic and objective outcome in patients who underwent reoperation because of failed antireflux surgery.Between 1990 and 2005, 130 patients (65 men and 65 women with mean age of 48,4 (14,1) years) underwent surgical reintervention because of failed antireflux surgery for GERD. Clinical data were obtained prospectively in all patients. Symptomatic outcome after reoperation was determined by sending a questionnaire to all patients. Postoperative esophageal manometry and 24-hour pH monitoring was performed to assess objective outcome. Outcome of abdominal and thoracic approached reoperations were separately analysed and compared.A total of 144 reinterventions were performed in 130 patients. A thoracic approach was used in 78 (54,2%) reoperations and an abdominal approach in 66 (45,8%) including 16 laparoscopic procedures. The thoracic group (TG) comprehended Belsey Mark IV fundoplications only and reoperations in the abdominal group (AG) included Nissen- and partial fundoplications. Indications for reoperation were recurrent reflux (45,8%), dysphagia (34,7%), a combination of both (12,5%), atypical pain symptoms (5,6%) or anaemia (1,4%). After a mean follow-up of 60,1 (37,2) months, 70,3% of patients rated their reflux disease as improved or resolved. The mean total esophageal acid exposure percentage decreased significantly from 8,8 (11,8) before reintervention to 3,6 (6,0) at follow-up. There were no statistical significant differences between the AG and TG with regard to symptomatic and objective outcome.Reoperative antireflux surgery has demonstrated to yield successful symptomatic and objective results in 70% of patients in this prospective cohort series, thereby signifying the effectiveness of this type of surgery for patients with initial unsatisfactory outcome.

CT investigation in CD 117 revised gastrointestinal stromal tumours (GISTs)

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Although complete surgical extirpation remains the only curative treatment of GISTs, introduction of tyrosinekinase inhibitors yields encouraging clinical responses in recurrent and metastatic disease. Many GISTs were not recognized in the past, but recently developed immunohistochemical markers have facilitated their diagnosis. We re-evaluated the pathological and clinical features of previously resected mesenchymal tumours of the gastrointestinal tract, after which patients were screened by abdominal and pulmonary CT scan. The aim of this study was to determine the accuracy of previous diagnoses and to investigate whether subsequent CT-investigations would reveal new (treatable) lesions in case of GIST.Patients with mesenchymal tumours of the gastrointestinal tract treated between 1987 and 2005 were identified using medical and pathology files. Tumours were pathologically reviewed using immunohistochemical staining for CD 117, CD 34, MIB 1, S100 and actine, a procedure which has been performed as a standard since 2002. Patients alive and identified as GISTs underwent pulmonary and abdominal CT-scans in order to identify individuals suitable for further (imatinib) treatment.41 Tumours have been identified as possible GISTs in this period. 32 Mesenchymal tumours of patients still alive were reanalyzed. Of these, 13 tumours had correctly been identified as GISTs. Pathological revision of the other 19, previously diagnosed as undefined gastrointestinal mesenchymal tumours, revealed GIST in another 8 cases. Therefore 21 of 32 (66 %) gastrointestinal mesenchymal tumours were shown to be GISTs. At surgery 19 GIST-patients underwent a R0 resection. In one patient a R2 resection was performed and in one patient the tumour appeared to be irresectable at time of operation. The latter two patients started imatinib immediately postoperatively. In 11 of the remaining 19 patients a CT-scan was not performed, mainly because of old age (>80 years). In 2 of the remaining 8 patients CT-scanning showed loco-regional and metastatic disease.Conclusions: The true incidence of GISTs was underestimated. Reviewing all mesenchymal tumours of the gastrointestinal tract using modern immunohistochemical techniques increased the number of detection. In GIST, follow-up schemes (even after reanalysis) using pulmonary and abdominal CT-scanning are valuable to detect loco-regional or metastatic disease which may respond to secondary surgical resection and/or imatinib treatment.

Laparoscopic adjustable gastric banding less successfull without follow-up

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Laparoscopic adjustable gastric banding is an effective therapy of achieving significant weight reduction in the morbidly obese. Major follow-up studies have shown a decrease in body-mass-index (BMI) of 10 Quetelet-points after laparoscopic adjustable gastric banding. Most follow-up studies however, fail to report the percentage of patients lost to follow-up. Our goal was to evaluate the difference in outcome between patients in regular follow-up and those lost to follow-up.Between October 1995 and May 2005, 411 patients (350 female, 61 male) underwent laparoscopic adjustable gastric banding for morbid obesity. Median age was 38 years (range: 17-60 years), median preoperative weight was 133,2 kg (range: 88,4-230,0 kg) and median preoperative BMI was 46,3 (36,2-84,3).The number of patients in regular follow-up was 358, with a median follow-up of 39 months. The number of patients lost to follow-up was 52. Out of this group 50 patients could be traced and weight outcome could be assessed.Median BMI loss after laparoscopic adjustable gastric banding in the group with regular follow-up was 10,2 Quetelet points. Median BMI loss in the group lost to follow-up was 2,1 Quetelet points. The difference between those two groups was significant ($p<0,05$).BMI loss after laparoscopic adjustable gastric banding was significant less in patients lost to follow-up compared to patients in regular follow-up. Compliance to follow-up is essential in the treatment of morbidly obese by laparoscopic adjustable gastric banding. When reporting outcome figures after laparoscopic adjustable gastric banding the percentage of patients lost to follow-up should be included.

Assessment of viable tumor tissue attached to needle electrodes after local ablation of liver tumors

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Introduction: Only a minority of patients with liver metastases are appropriate candidates for liver resection. Radiofrequency ablation (RFA) and interstitial laser coagulation (ILC) are useful ablative techniques to obtain local control of unresectable tumors. Needle track seeding (NTS) after local ablation of liver tumors has been reported between 0.9 and 12.5 per cent of cases and potentially affects long term survival. The aim of this study was to assess residual, viable tumor cells on needle electrodes after use in patients treated with RFA or ILC for liver tumors.
Methods: Forty-one patients, recruited among 7 centers, underwent 61 local liver ablation applications (47 RFA, 14 ILC) to treat 53 tumors (40 * RFA, 13 * ILC). Eleven applications were used for the ablation of 7 hepatocellular carcinomas (HCC) and 50 applications for the treatment of 46 liver metastases. Patient and tumor characteristics (histology, differentiation, size and location) were recorded as well as ablation characteristics, i.e. approach, type of electrode (non deployable electrode or laser fiber vs deployable electrode), ablation time and application of needle track ablation. Cells attached to the electrodes were analysed for viability and morphology by trypan blue test (TBT), hematoxylin & eosin, PAP and Giemsa staining.
Results: Macroscopic tissue adherence to electrodes was visible following 31 applications (50.8 %), only after use of the deployable electrode. Pathological detection of viable tumor cells was obtained in HE, PAP and Giemsa preparations after 4 applications (6.6 %). Positive TBT could be observed after 21 applications (34.4 %). Significant association ($p<0.05$) of the recorded parameters with increased risk of viable tumor attached to the needle electrode could be demonstrated in regard with three variables: i) poor differentiation of the primary colon tumor ii) the use of deployable RFA electrodes and iii) omission of needle track ablation after tumor ablation.
Conclusion: This study demonstrated the presence of viable tumor tissue adherent to needle electrodes after RFA. This finding advocates caution when locally ablating liver tumors and emphasizes the need for needle track ablation to prevent NTS, especially when using deployable RFA electrodes.

Liver volumetry plug and play: do it yourself with ImageJ!

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The remnant liver volume is a good indicator of the risk for liver dysfunction after major hepatectomy. As we showed before, it is possible to predict the volume of the liver remnant accurately by CT-volumetry using radiological image analysis software. This software however is typically linked to radiological hardware, making it less accessible for surgeons. ImageJ is a freely downloadable image analysis software package developed at the National Institute of Health, which may bring liver volumetry to the surgeon's desktop. The objective of the present study was to establish the accuracy for CT-volumetric analysis of the liver on a Personal Computer. ImageJ was downloaded from http://rsb.info.nih.gov/ij/. Preoperative CT scans of nine patients, who underwent liver resection because of primary or secondary liver malignancies, were retrospectively analyzed. CT-scans were opened in ImageJ and the total liver and the tumor were manually outlined on every slice. The resection specimen was outlined according to transection planes described in the operation notes. The area of each outline was multiplied by slice thickness to calculate liver volume. Volumes of resection specimens measured with ImageJ were compared with their weights, which were obtained during pathology examination. Correlation between weight and volume was determined with Pearson's test for correlations. There was an excellent correlation between resected liver volume calculated with ImageJ and actual weight of the resection specimen (r^2=0.99, $p<0.0001$). The mean (SEM) ratio between weight and volume (0.86 (0.03) g/ml) was in agreement with our earlier findings using CT-linked radiological software. Mean total liver volume was 1878 (215) mls, mean functional liver volume (total volume minus tumor volume) was 1701 (161) mls. Functional liver volume was significantly correlated with body weight (r^2=0.73, p=0.004) while total liver volume was not (r^2=0.36, p=0.09). The maximum CT-slice thickness that permitted accurate measurement was 1.0 cm.Conclusion. ImageJ can be used for CT-volumetric analysis of the liver, allowing an accurate estimation of residual liver volume after major hepatectomy on a Personal Computer. This application brings CT-volumetry to the surgeon's desktop and could be particularly useful in cases of tertiary referred patients, who already have a proper CT-scan on CD-rom from the referring institution.

Incidence and Management of Biliary Leakage after Partial Liver Resection

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Partial liver resection is effective treatment for patients with malignant and symptomatic benign hepatobiliary diseases. In literature, the incidence of postresection biliary leakage is reported to be 4.8-12% and is associated with substantial morbidity and even mortality. The aim of this study was to identify risk factors and to assess management and outcome of biliary leakage after liver resection in our center. Between January 1992-December 2004, 286 consecutive partial liver resections were performed. Patients who had undergone biliary reconstruction in conjunction with liver resection (such as in cholangiocarcinoma) were excluded from this analysis. Hence, the medical records of 234 patients were reviewed to identify patients with postoperative biliary leakage (defined as bile effluent from abdominal drain > 1 day after surgery, bile collection or leakage detected on radiological imaging or found during relaparotomy). Postoperative biliary leakage occurred in 6.8% (16/234) of patients. Patients with biliary leakage were mainly male (75 vs. 46%;P=0.037), showed longer postoperative hospital stay (35.4 vs. 15.9 days; P<0.001) and underwent more reoperations (25 vs. 3.2%; P=0.002) in comparison to patients without biliary leakage. On univariate analysis, major liver resection (≥ 3 segments)(P=0.004), prolonged operation time (P=0.001), right sided hemihepatectomy (P=0.005), tumor size (P=0.026), duration of vascular occlusion (P=0.030) and surgical irradicality (P=0.001) were risk factors. Multivariate analysis revealed only prolonged operation time as independent factor (P=0.013, OR=1.014). The site of biliary leakage was the resection surface in 63% (10/16 patients) and the extrahepatic bile ducts in 37% of patients.The biliary leakage was observed in 19% (3/16 patients) and resolved spontaneously. Endoscopic stent placement was performed in 9 (56%) patients and 4 patients were treated by percutaneous biliary drainage. Five patients required relaparotomy for evacuation of a bilioma.One patient (6.3%) with early biliary leakage eventually died of liver failure.Conclusion: In spite of improved techniques for parenchymal dissection, biliary leakage is a persisting complication after liver resection. Duration of surgical procedure was the only independent factor for post-operative biliary leakage. Percutaneous biliary drainage and endoscopic stenting are effective interventions in the management of most cases of biliary leakage after liver resection.

Pancreas preserving total duodenectomy for patient with familial adenomatous polyposis of the duodenum: a comparison with pancreatoduodenectomy

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Duodenal adenomatosis remains a leading cause of death in Familial adenomatosis polyposis (FAP) patients who have previously undergone colectomy. Many endoscopic and surgical approaches are available including the recently introduced pancreas preserving total duodenectomy (PPTD) and pancreatoduodenectomy (PD). A retrospective review was performed to analyze the results of for PPTD for FAP and compare the results with PD for neoplasms of the ampulla of Vater (considered to be relatively comparable since both diseases are generally limited to the duodenum) Between January 2000 and December 2004, all patients who underwent PPTD (n=20) in four academic centers in the Netherlands were included and compared with the cohort who underwent PD (n=63) for ampulla of Vater adenocarcinoma in the Academic Medical Center during the same time period. Patients who underwent PPTD were significantly younger compared to patients who underwent PD (51 years vs. 62 years, respectively, P<0.001). Patients who underwent a PPTD had Spigelman III (5%) and Sigelman IV (95%) disease at preoperative endoscopy. Median operative time was significantly longer in patients who underwent PPTD compared to PD (315 min. vs. 271 min., respectively, p= 0.014). Morbidity did not differ significantly (PPTD 75% vs. PD 57%, p= 0.513). Anastomtic leakage was the most common complication in both procedure (PPTD 35% vs. PD 25%, p= 0.405). The relaparotomy rate was comparable in both procedures (PPTD 20% vs. PD 19%, p= 1.000). Two patients in both groups died (PPTD 10% vs. PD 3%, p=0.224). During follow-up recurrence occurred in 20% of the patients after PPTD and in 16% of the patients after PD. The present study found that operative time for PPTD is significantly longer compared to PD and that, although not significant, PPTD had a trend towards a higher postoperative morbidity and mortality rate compared to PD.

Increased number of resections and more conservative management of patients with primary cystic neoplasms of the pancreas

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There seems to be an increase in the number of resections for primary cystic neoplasms of the pancreas. The aim of the study was to analyze whether the number of resections for primary cystic neoplasms of the pancreas increased and if changes in work-up and management have occurred throughout the years. A retrospective analyses of patients who underwent resection during January 1992 and December 2004 for primary cystic neoplasms of the pancreas was performed. Patients were divided into two groups with equal number of patients to analyze differences work-up and management strategies. Results: Overall, 90 patients had a primary cystic neoplasm of the pancreas and consisted of pathologically proven serous cystic neoplasms (n=25), mucinous cystadenomas (n=30), mucinous cystadenocarcinomas (n=15), intraductal papillary mucinous neoplasm (n=25) and solid pseudopapillary neoplasms (n=12). Forty four out of 419 resections (11%) were performed in the first 9 years of the study period and 46 out of 233 (20%) in the last 4 years (p= 0.001). There were significantly more patients referred in the recent period with incidentally found cyst (14% vs. 39%, respectively, p=0.006). Computed tomography use was not significantly different in both periods (77% vs. 93%, respectively, p= 0.310) supplemented by endoscopic ultrasonography (5% vs. 33%, respectively, p=0.001) in the recent period. There were significantly less splenectomies preformed for left pancreatectomies in the recent period (86% vs. 47%, respectively, p= 0.011). Morbidity was comparable in both periods (27% vs. 46%, respectively, p=0.060). One patient died out of 90 patients (1%). The number of resections for primary cystic neoplasms of the pancreas has nearly doubled to 20% of al resection for pancreatic neoplasms in the recent years and more patients are referred with incidentally detected neoplasms. The diagnostic work-up consisted mostly of CT scanning. The spleen is successfully preserved more often when a left pancreatectomy is preformed while the postoperative morbidity and mortality have not changed throughout the years. Finally, the medium-term outcome is favorable. Unfortunatly, a large portion of patients with serous cystic neoplasms and no symtoms underwent resection because the work-up could not differentiate between this benign disease and potentially malgnant disease.

Pancreaticoduodenectomy without preoperative radiological and histological diagnosis. Diagnostic strategy/managemen

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Introduction: There is still controversy about the diagnostic strategy and management of patients with clinical suspicion of a pancreatic/periampullary tumour (stenosis of CBD) but without a 'visible mass' noticed on US, CT or MRCP. In these patients EUS and/or brush/biopsy as additional diagnostic workup might be helpful in deciding whether or not surgery is indicated.
Objective: The present study evaluated the additional value of EUS and brush/biopsy in the diagnostic workup of patients with inconclusive preoperative radiological imaging. Final pathology after resection was correlated with preoperative diagnostic results.
Methods: A consecutive cohort of 303 patients, suspected to have a pancreatic/-periampullary malignancy, underwent pancreaticoduodenectomy from January 2000 to October 2005. Patients were classified by results of preoperative diagnostic workup: (A) visible mass on US/CT/MRCP, (B) no visible mass but conclusive additional diagnostic workup, (C) no mass and inconclusive results of additional diagnostic procedures or without further diagnostics performed. Final pathological findings after resection were correlated with preoperative diagnostic results.
Results: A mass was confirmed by US/CT/MRCP in 231 patients (group A: 76.2%). Of the 72 patients without a visible mass in 62 (86.1%) EUS and/or brush/biopsy had led to a preoperative diagnosis (group B: 20.5%), while the remaining 10 patients also had inconclusive results of additional diagnostic workup or no further diagnostics performed (group C: 3.3%). Pathological findings after resection were, overall and for each group separately (A/B/C): (pre)malignancy 87.9% (88.7/85.5/50), benign 1.6% (2.6/1.6/8.3), chronic pancreatitis 9.9% (8.7/11.3/30), no tumour 0.7% (-/1.6/8.3). CONCLUSIONS: In patients clinically suspected to have a pancreatic/periampullary tumour, 76.2% showed to have a mass on US, CT or MRCP of which 89% had a (pre)malignancy at pathology. In the remaining 23.8% additional diagnostic workup through EUS and/or brush/biopsy leads in 86.1% of the cases to a preoperative diagnosis. In the very small subgroup of patients clinically suspicious of having a pancreatic/periampullary tumour, but without conclusive preoperative diagnostics, 50% appears to have a malignancy after resection.

Incidence of Focal Pancreatitis after pancreatoduodenectomy and the differentiation based on the clinical presentation and imaging.

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Differentiation between patients with a pancreatic head mass based of focal pancreatitis (FP)and pancreatic adenocarcinoma (PCA) can be very difficult. Differentiating is import since patients who suffer from chronic pancreatitis are generally treated with a pancreas preserving procedure. The aim of the present study was to analyze the incidence of focal pancreatitis after pancreatoduodenectomy for suspected malignant lesions and the clinical and imaging features. Out of a consecutive group of patients (n=570) who underwent pancreatoduodenectomy between 1992 and 2004, in the Academic Medical Center, patients with histopathologically proven FP and PCA were selected and clinical and imaging characteristics were analyzed. The other neoplasms were excluded because these are generally not confused with FP. The incidence of focal pancreatitis after pancreatoduodenectomy which was not diagnosed preoperatively is 58 out of 570 patients (10.2%). Pancreatic adenocarcinoma occurred in 195 patients (34%). Patients with FP were significantly younger compared to patients with PCA (55 years vs. 64 years, respectively, P< 0.001) and predominantly male (74% vs. 48%, P=0.001). The number of patients with diabetes, weight loss and the alcohol consumption was not different in both groups. Patients with FP complained significantly more often of pain compared to patients with PCA (78% vs. 40%, respectively, P< 0.001). Jaundice occurred significantly more often in patients with PCA compared to FP (92% vs. 67%, respectively, p<0.001). All patient had a pancreatic mass. The size of the lesion was comparable for FP and PCA on US (3.0 cm. vs. 2.8 cm., respectively, p=0.424) and CT (2.0 cm. vs. 2.5 cm., resectively, p=0.257). The presence of a double duct sign on ERCP occurred equally in both groups. All other patients had a dilated bile duct. The radiological details (e.g. calcifications) will be presented in detail. Morbidity occurred in 45% of the patients after resection for FP and 46% of the patients after resection for PCA. Mortality was nil in both groups. Data concerning the pathology of the patients who suffered from auto-immune pancreatitis will be presented at the meeting. The incidence of FP for patients undergoing PD for a suspected leasion of the pancreatic head is 10.2%. Focal pancreatitis is associated with some presenting symptoms (younger, male patients presenting with pain and without jaundice) but differentiation remains difficult.

Endoscopic and Surgical therapy is successful after complicated End to End Anastomosis in Bile Duct Injury patients

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An end to end anastomosis (EEA) (with or without T-tube drainage) in bile duct injuries is reported to be associated with a high incidence of recurrent jaundice due to stricture formation of the anastomosis area. Endoscopic stenting is the management of choice for postoperative bile duct stenosis.Patients referred to a tertiary center after previous EEA will represent the worst selection of the population treated with EEA. The aim of this study was to evaluate the long term outcome in this selected group of patients with complications of a primary EEA. Of a total of 500 BDI patients referred between 1991 and 2005, 56 patients (11.2%) were referred after a primary EEA. In 42 patients (75%) a complete transsection was diagnosed during the initial operation. In 49 patients (87%) the anastomosis was performed over a T-tube, and a peroperative cholangiography was performed in 24 patients (43%). Median duration of T-tube drainage was 42 days, range 2-145. Patients were referred after a median of 16 weeks (range 0 – 141) after the initial operation. The indication for referral was leakage in 10 patients (18%) and biliary obstruction in 46 patients (82%). After referral 43 (77%) patients were initially treated endoscopically or by percutaneous transhepatic stent placement (n=3, 5%). After a mean follow up of 7 ± 3.3 years, 37 patients (66%) were successfully treated with dilatation and endoscopically placed stents, median duration 364 days range 36-1355, median stent replacements 6, range 2-15. One patient died 4 years after the initial operation due to complication related to the endoscopic treatment. A total of 18 patients (32%) underwent a hepaticojejunostomy, in 5 patients (9%) because initial treatment failed and in 13 patients (23%) primary reconstructive surgery was performed. Post operative complications occurred in 3 patients (5%). Leakage of the anastomosis (n=1) was treated by percutaneous transhepatic stent and in two patients a stenosis of the secondary anastomosis was successfully treated with a percutaneous transhepatic dilatation.An end to end anastomosis might be considered as a primary treatment for BDI because even complications (stricture or leakage) can be adequately managed by endoscopic or percutaneous drainage in 66% and reconstructive surgery after EEA is a procedure with acceptable morbidity and no mortality.

Evaluation of available scoring systems to predict ongoing intra-abdominal infection in patients with secondary peritonitis and the need for relaparotomy.

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To date there is no reliable scoring system that aids the decisional process by predicting relaparotomy outcome for patients with abdominal sepsis after the emergency (index) laparotomy. Scoring systems designed for ICU patients in general, APACHE II and Mannheim Peritonitis Index (MPI) at baseline, and the sequential Multiple Organ Dysfunction Score (MODS) and Sequential Organ Failure Assessment (SOFA) score, were analyzed for predicting outcome of the first relaparotomy rather than outcome of disease only. Positive findings at relaparotomy were defined as persistent peritonitis or a new infectious focus recorded by the operating surgeon.The study population consisted of the planned arm of patients of the RELAP trial (n=96), to assure a homogeneous group of peritonitis patients. All received a relaparotomy between 36 and 48 hours after the index laparotomy. Findings were related to the APACHE II and MPI scores after the index operation and the median 48-hour post-index MODS and SOFA scores. The overall probability for positive findings was 55/96 (57%). The median APACHE II, MPI and 48 hour-MODS scores did not differ significantly for positive or negative findings (APACHE II: 15.0 and 16.0, resp; MPI: 25.5 and 21.8, resp, and MODS 4.0 in both groups). Although the APACHE II and the MODS did not predict positive findings (OR 0.95, 95%CI 0.9–1.0, P=.250 and OR 0.9, 95%CI 0.7–1.0, P=.135, resp), the MPI did (OR 1.3, 95%CI 1.2–1.5, P<.001). This translated into a 30% increase in odds for positive findings per point increase in MPI.The APACHE II and the MODS predicted in-hospital mortality (OR 1.3, 95%CI 1.2– 1.5, P<.001 and OR 1.5, 95%CI 1.1–1.9, P=.003) where the MPI failed to predict final outcome of disease (OR 1.1, 95%CI 0.99–1.1, P=.120).The predictability of the SOFA score was comparable to that of the MODS. In conclusion only the MPI was of value in predicting ongoing abdominal infection at relaparotomy in the early phase of abdominal sepsis. However, it did not predict final outcome of disease, which may indicate that the included peritonitis covariates are not good predictors for survival. The MPI is based on a single time point measurement and not equipped for sequential evaluation. This makes the development of a longitudinal and cross-sectional scoring system to aid in the decision during the course of disease who en when to re-operate a high priopriority issue. APACHE II and baseline MODS are good predictors for in-hospital mortality

Intestinal permeability is associated with severity of disease in surgical ICU patients.

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Increased intestinal pemeability is proposed to be the motor of sepsis in surgical critical care patients. It is thought that the surgical stress and hypoxia induce a loss of intestinal barrier function and therefore predispose for bacterial translocation. Sugar absorption tests have produced a wide variation in results. Poly-ethylene glycols (PEGs) of various molecular mass have been used as markers for intestinal permeability in non critically ill patients. PEG 400 can freely pass the intestinal mucosal barrier, larger PEGs can only pass when intestinal permeability is compromised. We investigated whether the intestinal permeability, as measured with PEGs, is associated with the severity of disease in surgical ICU patients.Thirty-seven surgical ICU patients were included (mean APACHE II score 14 ± 5.5). The patients ingested a solution of 5g PEG 400, 1.5g PEG 1500, 5g PEG 4000 and 10g PEG 10000 dissolved in 100 ml water within the first 48 hours of admission. Urine was collected in the following 12 hours and analyzed for PEG by HPLC. The test was repeated every other day during the first two weeks of ICU stay. PEG values from the ICU patients were compared with control values from an earlier validation study. Severity of organ failure was assessed by the SOFA score. Data are presented as the intestinal permeability index (IPI for PEGi = (PEGi / PEG 400) x 100%). Statistical analysis was performed using t-test and logistic regression. The IPI for PEG 1500 increased from 1.79 (± 0.39 mean ± SEM) in controls to 3.90 (± 1.60) in surgical ICU patients on admission (P = 0.031). The IPI for PEG 4000 increased from 0.20 (± 1.59) in controls to 0.52 (± 0.16) in surgical ICU patients on admission (P = 0.040). A significant increase in the IPI for PEG 1500 on day 4 was found between patients who developed severe organ failure and patients who did not (P = 0.034). The IPI for PEG 1500 correlated with the SOFA score (P = 0.012) as it changed during the period of ICU stay, when corrected for stomach retention and creatinin levels. In conclusion these data suggest an association between intestinal permeability and the course of disease, because 1) intestinal permeability of surgical intensive care patients was increased compared to healthy controls, 2) intestinal permeability on day 4 correlated with the development of organ failure and 3) changes in intestinal permeability correlated with changes in severity of disease over time.

Non-elective colectomy in patients with fulminating colitis A systematic review of the literature

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Fulminant colitis in patients with inflammatory bowel disease is known to be a very serious condition requiring aggressive treatment, either medical, surgical or both. The aim of this study was to define the possibilities for improvement of outcome in patients with fulminating colitis operated on in a non-elective (emergency or urgent) setting through analysis of their early outcome after colectomy. Medline and PubMed databases were searched for studies (1975-2005) regarding mortality and morbidity after colectomy in IBD patients with fulminating colitis. Criteria of in- and exclusion were set. Eligibility of studies was assessed through a modification of the methodological index for non-randomized studies (MINORS). Data extraction was pointed out in advance. The data were divided in three decades according to year of publication. Statistical analysis was performed. The abstracts of 1261 articles were studied. Application of the in- and exclusion criteria and methodological assessment left 29 articles for inclusion. The pooled patients data comprised a total population of 2714 patients, of whom 1257 were operated on in a non-elective setting. 30-day mortality was 5.2%, in-hospital mortality was 8.0%. Overall morbidity was 50.8%. The majority of complications were of infectious or thromboembolic nature. There was a significant shift in indications for colectomy over the three decades. The incidence of toxic megacolon and perforation decreased, whereas fulminant colitis increased over time. A significant reduction in adverse outcome was found in this thirty year time span. There was no significant difference in mortality and morbidity between subtotal colectomy and proctocolectomy.Conclusion: Urgent and emercency (procto-) colectomy for fulminant colitis are complicated by high mortality and morbidity. Main complications are of infectious and thromboembolic origin. Improvement of results is to be achieved by dealing with each of these. Several suggestions to optimize outcome are made.

Systematic review of short-term outcomes after laparoscopic ileocolic resection for Crohn's disease

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No consensus exists whether ileocolic resection for Crohn's disease (CD) should be carried out by a laparoscopic or open approach. A systematic review was undertaken to assess the evidence of short-term advantages of a laparoscopic approach compared to an open approach in patients undergoing ileocolic resection for CD.A systematic search of the literature was conducted over the period January 1991 up to Januari 2006. Only randomised controlled trials (RCTs), clinical controlled trials and comparative studies that compared laparoscopic with open resection for ileocolic CD were included. A quality assessment as proposed by the Dutch Cochrane Collaboration was done for all retrieved full-text articles. Primary outcome parameters were operating times, conversion rates, major and minor morbidity and hospital stay. A total of 14 publications encompassing 729 patients met the inclusion criteria. Two were randomised controlled trials, both of moderate to good quality, and 12 were non-randomised controlled trials (non-RCTs) of generally fair quality. Pooling the data of operating times was not possible due to statistical heterogeneity, but operating times were longer for the laparoscopic procedure in the individual studies. The conversion rate varied between 0 and 16.7%. A meta-analysis of the number of postoperative complications requiring re-operation or reported overall morbidity showed no difference between both procedures (risk difference -0.01 and -0.05 respectively). Hospital stay after the laparoscopic procedure was reduced by 1.90 days (CI: 0.83 - 2.97). Conclusions: There is evidence that laparoscopic ileocolic resection for CD is associated with shorter hospital stay compared to conventional open ileocolic resection, while morbidity rates are equal and conversion rates are acceptable.

Molecular characteristics of small bowel carcinomas vary with location

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Primary carcinomas of the small intestine are rare and their carcinogenesis remains poorly understood. The most frequent site of development is the duodenum (± 50 %), followed by the jejunum (± 25%) and the ileum (± 13%). It is not known whether the process of carcinogenesis differs in the different parts of the small intestine.The aim of this study is to elucidate the genetic pathways leading to the development of small intestinal carcinomas by immunohistochemical comparison of several candidate proteins in tumors of the duodenum, jejunum and ileum.The duodenal carcinomas (n = 20), jejunal carcinomas (n = 14) and ileal carcinomas (n = 6) were compared on Tissue Microarrays by immunohistochemical staining for the cytokeratins (CK7, CK20), DNA mismatch repair proteins (MLH1, MSH2, MSH6, PMS2), cell cycle proteins (P16, P53, cyclin D1), cell adhesion proteins (beta-catenin, E-cadherin, Ep-CAM) and SMAD4, CO-TL1, CEA.In the majority of carcinomas (more than 90%) invasion through the bowel wall was present (T3/T4). Most tumors were adenocarcinomas, the exceptions being 1 signet ring cell carcinoma in the duodenum, 1 mucinous carcinoma and 1 adenosquamous carcinoma in the jejunum and 1 mucinous carcinoma in the ileum. Approximately 50% of these tumors were poorly/undifferentiated. Both CK7 and CK20 were differentially expressed along the small bowel; with CK7 positivity in 63%, 28% and 0% and CK20 negativity in 35%, 15% and 0% of the carcinomas of the duodenum, jejunum and ileum respectively ($p = 0.01$, $p = 0.06$). P53 was overexpressed in 32%, 79% and 100% of the duodenal, jejunal and ileal carcinomas respectively ($p = 0.002$). Moderate to high loss of extracellular E-cadherin was seen in 75% and 92% of the carcinomas of duodenum and jejunum respectively in comparison to 33% of the ileal carcinomas ($p = 0.02$). Conclusions: Overexpression of P53 is less frequent in the duodenal carcinomas compared with more distal small bowel carcinomas. Differential expression of both CK7 and CK 20 reflects preexisting differences between the upper gastrointestinal tract and the colon. We propose that in the proximal small bowel carcinogenesis reflects gastric carcinogenesis, while in distal small bowel carcinogenesis resembles colonic carcinogenesis.

Small bowel carcinomas; an immunohistochemical comparison of sporadic, Familial Adenomatous Polyposis and Celiac disease related tumors

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Small bowel carcinomas account for only 1-5 % of the gastrointestinal malignancies and their carcinogenesis pathways remain poorly understood. However, patients with familial adenomatous polyposis (FAP) or celiac disease are known to have a high risk for the development of these tumors. In patients with FAP, the prevalence of duodenal carcinoma is 2-5 %. For patients with celiac disease, the risk for development of small bowel carcinomas is approximately tenfold higher as compared with the general population.The aim of this study is to elucidate the pathways leading to the development of small intestinal carcinomas by immunohistochemical comparison of candidate regulatory proteins in tumors of sporadic patients, patients with FAP and patients with Celiac disease. On Tissue Microarrays, the small bowel carcinomas of sporadic patients (n = 42) were compared with patients with FAP (n = 6) or celiac disease (n = 3) by immunohistochemical staining for the cytokeratins (CK7, CK20), DNA mismatch repair proteins (MLH1, MSH2, MSH6, PMS2), cell cycle proteins (P16, P53, cyclin D1), cell adhesion proteins (beta-catenin, E-cadherin, Ep-CAM) and SMAD4, CO-TL1, CEA.Tumors in the small bowel were present in an advanced stage (T3/T4 in more than 80%). In patients with celiac disease, only adenocarcinomas were observed. In patients with FAP, 17% were adenosquamous carcinomas and 50% of these tumors were poor/undifferentiated. In patients with sporadic tumors, in addition to adenocarcinomas, mucinous carcinomas (7%) and signet cell carcinomas (2%) were observed and 49% of these tumors were poor/undifferentiated. Absence of expression of both MLH1 and PMS2 was found in 2/3 of the Celiac disease related tumors, compared to 0% and 5 % in FAP and sporadic tumors, respectively ($p < 0.0001$). Overexpression of P53 was observed in 100% of the patients with celiac disease, compared to 17% of the tumors from patients with FAP and 58% in sporadic tumors ($p= 0.04$). No differences in the staining of the other candidate proteins were observed in the three groups of tumors.Conclusions: The majority of cancer-related proteins did not differ in expression between the three types of small intestinal tumors. Celiac disease-related carcinomas showed an overexpression of P53 as well as absence of DNA mismatch repair proteins, MLH1 and PMS2, suggesting that carcinogenesis in these patients follows a different pathway as compared to sporadic or FAP related small intestinal tumors.

Prevalence of adenomas and carcinomas in the ileal pouch in patients with familial adenomatous polyposis.

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At present, more than half of patients with FAP are treated with a proctocolectomy and an ileo-pouch-anal anastomosis (IPAA). Originally, it was thought that this procedure would eliminate the risk of developing bowel cancer. However, an increasing number of studies report the development of adenoma in the pouch. Moreover, several case reports of pouch carcinomas have been published. The aim of this study was to evaluate the long-term risk of developing an adenoma or carcinoma in the pouch in a large cohort of Dutch FAP patients. 254 patients with FAP from the Dutch Polyposis Registry were analyzed. Information on the surveillance examinations was obtained from medical reports. All pathology reports were collected. Full information on follow up was available in 212 (56% male) of the 254 patients. These patients underwent a total of 761 endoscopies. The mean follow up was 7.9 years (range: 0.4 – 20.3 yrs). In 13 subjects the pouch was resected during follow up: in four cases because of a pouch carcinoma, in two because of the development of adenomas, in one because of stenosis and in five cases because of severe dysfunction of the pouch. The cumulative risk of developing an adenoma at ten years follow up was 45%. Twenty-five patients (11.8%) developed an adenoma with advanced pathology and four (1.9%) a carcinoma in the pouch. The cumulative risk of developing a pouch carcinoma at 10-years follow-up was 1%. The median interval between the detection of pouch cancer and the previous surveillance endoscopy was 25 months (range: 6-54 months). Conclusions: This study indicates that the risk of developing adenomas in the pouch after an IPAA is substantial, but that the risk of malignant degeneration appears to be low.

Risk analyses for sigmoidoscopy as a screening tool based on the incidence of proximal colorectal carcinomas in a general hospital

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Sigmoidoscopy screening for colorectal cancer (CRC) seems valuable. Colonoscopy may be more effective in CRC prevention, however colonoscopy requires more endoscopy facilities, has a higher risk of complications and is more expensive. The aim of this study was to determine the risk for advanced proximal neoplasia and to identify subgroups in which screening sigmoidoscopy might suffice using retrospective colonoscopy data from a single general hospital. A database search using the Endobase® datasystem was performed on all patients who underwent lower endoscopy between 1997 and October 2005 in a single general hospital. All patients diagnosed with CRC were included. Variables including age (< 65 or > 65 years of age), sex, and distal findings were used for risk analyses.In total 787 patients were diagnosed with CRC (M/F 413/375, mean age 70 yrs, range 27-95 yr). The CRC was localized in 67% of the patients in the distal colon and in 33% proximal of the descending colon. In the group under 65 years of age, in total 258 patients were diagnosed with CRC (149 M, 109 F). In 65/258 (25%) patients the CRC was localized in the proximal colon, without significant difference between men and women. A synchronous distal neoplasia was found in 21 of these 65 patients (12 M, 9 F). In 17% (44/258) only a proximal CRC was found, which would have been missed by screening sigmoidoscopy. In the group over 65 years of age, 536 patients were diagnosed with CRC (267 M, 269 F). In 198/536 (37%) patients the CRC was localized in the proximal colon, significantly more women had a proximal CRC (75 M, 123 F, $p<0.01$). A synchronous distal neoplasia was found in 44 of these 198 patients (22 M, 22 F). In 29% (154/536) only a proximal neoplasia was found, which is significantly more compared to those under 65 yrs of age ($p<0.01$). In conclusion, the proportion of CRC that is located in the proximal colon changes with age. In patients above 65 yrs of age, proximal CRC is proportionally more common, and more often occurs without distal marker lesions and thus would have been missed by sigmoidoscopy screening. When considering CRC screening sigmoidoscopy will suffice in the age group below 65 yrs of age. Given these data, in men and women above 65 yrs of age colonoscopy might be the preferred screening method.

Quality of life after Transanal Endoscopic Microsurgery and Total Mesorectal Excision in early rectal cancer

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Background and aimsTotal Mesorectal Excision (TME) is the gold standard in rectal cancer, if curation is intended. Transanal Endoscopic Microsurgery (TEM) has comparable oncological results in early rectal cancer. Impact of both procedures on quality of life (QOL) has never been compared. In this study we compared QOL after TEM and TME.Patients and methods54 Patients underwent TEM for T1 carcinomas. Only patients without known locoregional or distant recurrences were included, resulting in 36 eligible patients in whom quality of life after TEM was studied. The questionnaires used were the EuroQol EQ-5D, EQ-VAS, EORTC QLQ-C30 and EORTC QLQ-CR38. The results were compared to a sex-and age-matched sample of T+N0 rectal cancer patients who had undergone sphincter saving surgery by TME and a sex- and age matched community-based sample of healthy persons.ResultsThe overall response rate was 86%. Quality of life from the patients' and social perspective differed not between the groups. Compared to TEM, significant defecation problems were seen after TME ($p < 0.05$). A trend towards better sexual functioning after TEM, compared to TME, was seen, especially in male patients, although it did not reach statistical significance.
Conclusion: TEM and TME do not differ in QOL postoperatively, but defecation disorders are morefrequently encountered after TME. This difference could play a role in the choice of surgical therapy in (early) rectal cancer.

The Diagnostic Value of the Proton Pump Inhibitor Test for Gastroesophageal Reflux Disease: A population-based study

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Introduction: General practice guidelines often suggest as diagnostic tool for GERD the symptomatic response to a short course of proton pump inhibitor (PPI test). Our aim was to re-determine the diagnostic abilities of the PPI test by using the most relevant reference test, the symptom association probability (SAP), in a primary care population.
Methods: Subjects suspected of GERD who had heartburn complaints for at least twice a week during at least 3 months were recruited from primary care, either during consultation or by advertisement. After a 24h pH recording with calculation of the SAP, subjects started using 40 mg esomeprazole once daily for 13 days. The PPI test was considered positive when the subjects reported that their symptoms were adequately suppressed. Sensitivity, specificity and positive likelihood ratios were determined for each PPI test day. Data are presented as median values with interquartile ranges (IQR).
Results: In total 90 subjects were included (1/3 consultation, 2/3 advertisement). Successful 24h pH recording was accomplished in 84 subjects and the SAP was calculable in 74. The median age was 51 yr (IQR 41- 62), and 62% was male. The SAP was positive in 70% of the subjects. The sensitivity of the PPI test was 92.2% (IQR 87.4-93.5) and the specificity was 28.6% (IQR 19-33.3). The likelihood ratios were low (1.3 (IQR 1.2-1.4)) with little variation over the 13 consecutive PPI test days.
Conclusion: The sensitivity of the PPI test for diagnosing GERD is high, but its specificity low. The low likelihood ratios observed from day 1 to day 13 indicate that the PPI test does not change the high pre-test probability (70%) of GERD found in primary care patients with heartburn. The additional value of short term treatment with proton pump inhibitors for diagnosing GERD in primary care is relatively poor even with the most adequate reference test SAP.

Characteristics of gastro-oesophageal reflux in symptomatic patients with and without excessive distal oesophageal acid exposure

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In a subset of GORD patients a positive relationship between symptoms and reflux episodes can be demonstrated in the absence of excessive distal oesophageal acid exposure. It is assumed that hypersensitivity of the oesophagus to acid plays an important role in these patients. Besides acidity of the refluxate other factors such as its proximal extent may determine whether a reflux episode is perceived or not. The aim of this study was therefore to investigate the profile of reflux episodes in GORD patients without excessive distal oesophageal acid exposure.Combined 24-hr impedance and pH monitoring was performed in 14 GORD patients with excessive reflux (pH+), 14 GORD patients with physiological reflux (pH-) and 14 controls. All patients had a positive symptom-reflux association during 24-hour reflux monitoring.We found an oesophageal acid exposure time of 9.8% in pH+ GORD patients compared to 3.5% in the pH- patients and 2.9% in the controls. The incidence of acid reflux episodes in pH- patients (25.5 ± 4.9) and controls (20.2 ± 3.9) was comparable but significantly lower ($p<0.05$) than the incidence in pH+ patients (69.8 ± 7.3). However, no differences in the number of weakly acidic reflux episodes were observed between pH- GORD patients, pH+ GORD patients and controls (27.2 ± 3.8 vs 26.8 ± 4.6 and 21.0 ± 3.7, respectively). The proportion of reflux episodes that reached the proximal oesophagus was significantly higher in the pH+ GORD patients (19.6 %) and pH- GORD (17.8 %) patients than in the controls (5.7 %, $p<0.05$). Of the 158 symptomatic reflux episodes in the pH+ GORD patients 53 (33.5%) were due to reflux episodes that reached the proximal oesophagus. Of the 55 symptomatic reflux episodes in the pH- GORD patients, 21 (38.2%) were due to reflux episodes that reached the proximal oesophagus. We conclude that not only in GORD patients with excessive reflux but also in those with a normal distal oesophageal acid exposure a higher proportion of reflux episodes reaches the proximal oesophagus than in controls. These findings suggest that not only oesophageal hypersensitivity but also proximal extent may play a role in symptom generation in GORD patients without excessive reflux.

Involvement of cannabinoid receptors in the triggering of TLESRs in healthy subjects

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Background/ Aims: Transient Lower Esophageal Sphincter Relaxations (TLESRs) are the main mechanism underlying gastroesophageal reflux and are a potential target in the treatment of gastroesophageal reflux disease. Previous animal experiments have showed that activation of cannabinoid (CB1) receptors reduces the occurrence of TLESRs. To determine whether these receptors also control TLESRs in humans, we evaluated the effect of the CB receptor agonist delta-9-tetra-hydrocannabinol (THC) on meal induced triggering of TLESRs in healthy volunteers.
Methods: The effect of THC (marinol ® 10 and 20 mg, p.o.) was evaluated on the occurrence of postprandial TLESRs in a randomized double blind placebo controlled study. On 3 different study days, 18 healthy volunteers (19-51, M) underwent combined esophageal manometry / pH metry using a 10 channel water perfused sleeve catheter. TLESRs were evoked by meal ingestion. Basal LES pressure was determined as visual means of one minute periods every 15 minutes. Samples for plasma concentration measurements were collected. For statistical analysis, paired Student's t-tests were used and data is presented as mean ±SE, except the number of TLESRs which are presented as median and interquartile range.
Results: All subjects tolerated the lowest THC dose. However, due to nausea and vomiting in the first hour after meal intake, only 8 subjects completed the 20 mg THC session. Meal ingestion resulted in an increase in TLESRs mainly during the first postprandial hour. This increase was dose dependently inhibited by THC compared to placebo (placebo 8.0 (6.0-9.3); THC 10 mg 5.0 (3.8-7.0); THC 20 mg 2.5 (0.0- 7.3), $P<0.018$). No significant effect was observed in the second and third postprandial hour. In addition, THC 10 mg significantly reduced basal LES pressure at every measured time point during the first postprandial hour compared to placebo (mean LES pressure at 45 min after meal intake: placebo 12 ± 2 mmHg; THC 10 mg 6 ± 1 mmHg ($P<0.011$); THC 20 mg 5 ± 1 mmHg (NS)). The number of acid reflux episodes did not differ between THC and placebo (placebo 4 ± 1; THC 10 mg 4 ± 1; THC 20 mg 3 ± 1 (NS)).
Conclusion: THC significantly reduces basal LES pressure and inhibits the increase in TLESRs evoked by meal ingestion. Based on these findings, we conclude that CB receptors are involved in the triggering of TLESRs in humans.

Effect of distraction and attention on the frequency of belching in patients with aerophagia

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In patients with excessive belching (aerophagia) an organic cause is seldom found and a psychogenic cause is often suspected. Aim of this study was to investigate the effects of attention and distraction on the frequency of belching.In 10 patients with aerophagia oesophageal manometry and impedance monitoring was performed for 2 hours. These 2 hours consisted of 4 30-min recording periods. Period 1: patient unaware of recording. Period 2: patient informed of recording. Period 3: patient distracted by filling in questionnaires. Period 4: patient not distracted. One patient stopped belching immediately after introduction of the catheters and was excluded from further analysis. In the remaining 9 patients, a total of 1258 belches was measured, 51 (4%) of which were the result of air that escaped from the stomach (gastric belches). The remaining 1207 belches (96%) were events during which air was expelled in oral direction almost immediately after entering the oesophagus, before reaching the stomach (supragastric belches). Gastric belches were distributed equally over the first (1.5 (0.5-2.0)), second (1.5 (0.5-2.0)), third (1.0 (0-2.0)) and fourth (1.0 (0-2.0)) recording period. In contrast, the incidence of supragastric belches increased significantly ($p<0.05$) from 0 (0-32) in the first period to 30 (18-60) in the second period, after patients were told that recording was started. During the questionnaires the incidence of supragastric belches decreased ($p<0.05$) to 14 (4-30). In the fourth period the incidence of supragastric belches increased ($p=0.08$) to 21 (10-49). Supragastric belches were initiated either by sucking air into the oesophagus by a negative thoracic pressure (8 patients) or by injecting air into the oesophagus by a pharyngeal contraction (2 patients).We conclude that the vast majority of belches in patients with aerophagia is due to supragastric belching. When patients are unaware that they are being studied or when they are distracted the incidence of belching is significantly reduced. This suggests that psychological factors are involved, supporting treatments such as behavioural therapy. The mechanisms the patients use to fill their oesophagus with air during supragastric belching are similar to the techniques described for facilitation of oesophageal speech in laryngectomized patients, suggesting that logopedic therapy might also be helpful.

The Manometric Common Cavity Phenomenon is an Unreliable Indicator of Gastroesophageal Reflux

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Introduction: The manometric common cavity phenomenon is characterized by a simultaneous intra-esophageal pressure rise to gastric pressure level and is considered indicative of gastroesophageal reflux. There are differences in opinions on the sensitivity and the specificity of the common cavity phenomenon as reflux detector as well as on nature of the reflux events that are associated with a common cavity. Therefore we tested the value of reflux detection by means of common cavity analysis using combined impedance and pH recording as reference standard. MethodsTen healthy male subjects (mean age 28 year range 20-46) underwent combined stationary pressure, pH and impedance recording for 4.5 hours. After 1.15 hours of recording, a reflux-eliciting meal was consumed (McDonald's Quarter Pounder hamburger, onions 20 grams, chips 44 grams, and orange juice 475 ml; total 967 kCal). A common cavity was defined as a pressure increase in at least two esophageal tracings to gastric level within 1s, remaining at that level for >0.5s. Reflux episodes were classified as liquid, mixed or gaseous reflux and the acidity of liquid and mixed reflux episodes was determined. The chi-square test was used for statistical analysis.ResultsA common cavity was found in 96 (43%) of the 223 reflux events detected by impedance, while 7 common cavities were unrelated to a reflux episode. In 54% of the reflux events detection of a common cavity was obscured by either contractile activity or artifacts caused by posture changes. The type of reflux associated with a common cavity (liquid 60%, mixed 31%, gas 9%) and without a common cavity (liquid 59%, mixed 29%, gas12%) did not differ, nor did the acidity of the reflux episodes (with common cavity: pH<4 67%, pH>4 33%; without common cavity pH<4 58%, pH >4 42%).
Discussion: The manometric common cavity phenomenon is specific but not sensitive as marker of gastroesophageal reflux. Furthermore, a common cavity is not specific for a particular type of reflux.

Relationship between impaired drinking capacity and intragastric distribution in patients with functional dyspepsia.

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A previous study demonstrated that the impaired drinking capacity in patients with functional dyspepsia (FD) could not be explained by altered proximal stomach function. To what extent abnormal distal stomach function or an altered intragastric distribution could explain the impaired drinking capacity in FD is unclear. Therefore, we determined gastric volumes after a drink test using SPECT imaging. After a baseline scan 20 HV (13f) and 18 FD (5f) underwent a drink test (100 ml/min) followed by SPECT scanning. A Mann-Whitney U test ($p<0.05$) was used for statistical analyses. Baseline gastric volumes measured by SPECT were significantly higher in FD compared to HV for total (351 ± 18 ml vs. 225 ± 18 ml; $p<0.001$), proximal (264 ± 9 ml vs. 184 ± 12 ml; $p<0.001$) and distal stomach (87 ± 12 ml vs. 41 ± 8 ml; $p<0.001$). FD ingested significantly less water compared to HV (1148 ± 143 ml vs. 1818 ± 153 ml; $p<0.001$). The gastric volume increase induced by the drink test was significantly different between HV and FD for total (2181 ± 149 ml vs. 1500 ± 140 ml; $p=0.006$), proximal (1671 ± 115 ml vs. 1266 ± 119 ml; $p=0.035$) and distal stomach (564 ± 48 ml vs. 234 ± 33 ml; $p<0.001$). There was a good correlation between the ingested amount of water and the increase in gastric volumes measured by SPECT (HV 0.61; $p=0.004$ and FD 0.88; $p<0.001$). The ingested water was differently distributed with proportionally more ingested volume in the distal stomach of HV compared to FD as illustrated by a difference in proximal/distal stomach volume ratio for FD compared to HV (6.4 ± 1.3 vs. 3.3 ± 0.4; $p=0.001$). Conclusion: These data suggest that drinking capacity is mainly determined by antral volume, with a reduced antral filling in FD compared to HV at maximal ingested volume. Whether this is due to an altered antral compliance or an increased antral sensitivity for distension remains to be studied.

Patients with Gastroparesis Have a Decreased Expression of the 5-HT4(C) Splice Variant in the Duodenum

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Background & Aims: Studies using 5-HT3 and 5-HT4 receptor agonists, selective serotonergic reuptake inhibitors (SSRI), and tryptophan depletion, have revealed that serotonergic signalling is involved in the regulation of gastric emptying rate and, potentially, in the generation of upper abdominal symptoms. To increase the understanding of the pathophysiologic basis of idiopathic gastroparesis at the molecular level, we compared the expression of genes encoding components of serotonergic signalling in the duodenum and stomach between patients with idiopathic gastroparesis and healthy controls.Methods: Mucosal biopsy specimens were collected from the duodenum, antrum, and fundus of 11 patients with idiopathic gastroparesis (2 male, mean age 46.5 ± 4.0 years) and 11 healthy controls (1 male, mean age 46.3 ± 2.5 years). Enterochromaffin (EC) cells (serotonin immunoreactive) were counted and mRNA levels of TPH-1 (the rate-limiting enzyme of 5-HT biosynthesis), SERT (regulates 5-HT availability by high affinity uptake), 5-HT3(C) and 5-HT3(E) (subunits of the 5-HT3 receptor), the 5-HT4 receptor, and three 5-HT4 splice variants (A, B, and C) were quantified by real time RT-PCR and compared between the two groups.Results: EC cell numbers were comparable in the three regions between the two groups. The expression of TPH-1 and SERT in all three regions was comparable between the groups ($P > 0.05$). In antrum and fundus, the expression of the 5-HT3 receptor subunits, the 5-HT4 receptor, and the 5-HT4 receptor splice variants was too low for accurate quantification. In the duodenum, the overall expression of the 5-HT4 receptor was comparable, however the 5-HT4(C) splice variant was expressed more abundantly in healthy controls compared to patients ($P = 0.015$). No differences were found in 5-HT4(A) or 5-HT4(B) expression. Finally, the 5-HT3 receptor subunits C and E showed comparable expression in both groups.Conclusion: These data suggest that delayed gastric emptying or the presence of upper abdominal symptoms does not result from altered 5-HT biosynthetic and uptake capacity or changed expression levels of the 5-HT3 and 5-HT4 receptor in the stomach and duodenum at the mucosal level. However, a different distribution of 5-HT4 splice variants, as shown by the lower expression level of the 5-HT4(C) variant, may cause a different functional response of 5-HT4 receptors upon stimulation and be of importance in the pathophysiology of gastroparesis.

i.c.v. infusion of semapimod ameliorates postoperative ileus in mice.

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Introduction: Peri-operative electrical stimulation of the vagal nerve (EVNS) shortens postoperative ileus (POI) in mice by reducing the inflammatory response triggered by intestinal manipulation. Previous studies in a sepsis model showed that this so-called cholinergic anti-inflammatory pathway can also be activated pharmacologically by central stimulation of the motor nucleus of the vagal nerve using i.c.v. injection of semapimod, a p38 MAPKinase inhibitor formally known as CNI-1493. Aim: To evaluate if central activation of the vagal nerve by i.c.v. semapimod reduces manipulation induced intestinal inflammation and shortens POI in mice. Methods: Mice underwent a laparotomy (L) or standardized intestinal manipulation (IM) 1. during sham or EVNS (left cervical vagal n., 5 V, 2 ms, 5 Hz) and 2. after 1μg/kg semapimod or saline i.c.v. 1 h prior to surgery. I.c.v. infusion was achieved through a cannula placed in the right lateral ventricle one week prior to the experiments. 24h after surgery, gastric emptying of a ^{99m}Tc-labled semi-liquid test meal was measured using scintigraphy. Intestinal muscle inflammation was assessed by MPO-positive cell count in ileal muscle wholemounts. A student t-test was used for statistical analysis. Values are depicted as mean ± s.e.m. $P<0.05$ was considered statistically significant. Results: IM significantly delayed gastric emptying 24h after surgery in sham treated mice (gastric retention at 80min (RT80) L= 8±2% vs. IM 36±7%, $p<0.05$, n=8) associated with inflammation of the manipulated intestine (MPO-pos. cell/mm^2, L= 21±11 vs. IM= 586±110, $p<0.05$, n=8). EVNS significantly reduced the number of MPO-positive cells and improved gastric emptying significantly (IM-EVNS: MPO-pos. cell/mm^2 227±55, $p<0.05$; RT80 20.0±3.2%, $p<0.05$, n=8). Similar to EVNS, pretreatment with 1μg/kg semapimod i.c.v. reduced the intestinal inflammation and enhanced gastric emptying compared to saline i.c.v. (MPO-pos. cell/mm^2 : saline 381±27 vs. semapimod 227±28, $p<0.05$; RT80: saline 19±4% vs. semapimod 8±0%, $p<0.05$, n=8).

Conclusion: Our findings show that central application of semapimod, like EVNS, reduces manipulation induced intestinal inflammation thereby shortening POI in mice. These data suggest that the cholinergic anti-inflammatory pathway to the intestine can also be activated pharmacologically by central application of semapimod. Future experiments, e.g. in vagotomized animals, are required to further unravel the mechanisms involved.

Alpha-7 selective nicotinergic agonist ameliorates postoperative ileus by inhibiting activation of intestinal macrophages

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Background. Post-operative ileus (POI) results from activation of intestinal macrophages due to bowel manipulation during surgical procedures. Vagus nerve-derived acetylcholine inhibits macrophage cytokine production by activating alpha-7 nicotinic receptors present on these cells. We previously showed that this anti-inflammatory pathway is mediated by transcription factor STAT3. Here, we evaluated the efficacy of nicotinergic agonists to ameliorate POI, and the cellular mechanism behind this effect.
Methods. Mice were treated with 1)vehicle, 2)nicotine (0.4 mg/kg), 3)AR-R1779 (a specific alpha-7 nicotinic agonist; 10 mg/kg) by i.p. injection. Thirty min thereafter mice underwent either control laparotomy (L) or intestinal manipulation (IM). Gastric emptying of a semi-liquid meal was determined by scintigraphic imaging 24 hrs after surgery. Myeloperoxidase (MPO) positive mononuclear cells were quantified in ileal muscularis of the manipulated region. Peritoneal macrophages were pre-treated *in vitro* with nicotine (0-10 uM), or AR-R1779 (0-10 uM) prior to challenge with LPS (10 ng/mL) and cell lysates were immunoblotted.
Results. In mice treated with vehicle, post-surgical (24hrs) gastric emptying (an indicator of POI) was significantly delayed in IM-mice compared to L control (gastric retention (%) at 80 min: 13.3 ± 2.7 (L) and 38.9 ± 9.7 (IM); $p<0.05$; n=8). Treatment with AR-R1779, but not nicotine, accelerated post-operative gastric emptying after IM, compared to saline (gastric retention (%) at 80 min: 30.7 ± 8.6 (nicotine), ns, 19.6 ± 4.4 (AR-R1779), $p<0.05$;n=8). Nor nicotine or AR-R17779 treatment affected gastric emptying after control L. In saline treated mice, IM was associated with a significant increase in MPO-positive cells in intestinal muscularis (50 ± 11 (L) *vs* 572 ± 112 (IM) cells/mm2, $p<0.05$). In mice pretreated with AR-R179, but not nicotine, the number of inflammatory cells recruited after IM surgery was reduced (cells/mm2: 395 ± 50 (nicotine); ns, and 231 ± 33 (AR-R1779); $p<0.05$, n=8). In LPS-stimulated peritoneal macrophages, nicotine and AR-R1779 dose-dependently activated the anti-inflammatory transcription factor STAT3.
Conclusion. The alpha-7 nicotinergic receptor agonist AR-R17779 activates STAT3 in intestinal macrophages and reduces manipulation-induced inflammation thereby ameliorating POI. Nicotine at the dose tested fails to reduce inflammation but higher doses may be required.

Non genomic transmission of visceral hypersensitivity across generations after maternal separation.

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Adverse parent-child interactions are associated with an increased risk to develop IBS later in life. Changes in maternal care induced by neonatal maternal separation (MS) in rats lead to altered stress responsiveness in the separated offspring, which can be transmitted across generations in a non-genomic fashion. Earlier, we showed visceral hypersensitivity to colorectal distension (CRD) in response to water avoidance (WA) stress in adult MS rats. Whether this hypersensitivity is also subject to non-genomic transmission is unknown.In order to investigate this question, female rats that underwent MS or were left undisturbed as a pup, were allowed to mate with non-handled (NH) male rats. The subsequent offspring was not subjected to MS. At the age of 3 months the offspring was equipped with EMG electrodes in the abdominal muscles to record the visceromotor response (VMR) to CRD. Visceral sensitivity was assessed by intermittent distention (1, 1.5, 2 ml) before and 24 hours after WA in male animals only. Post-WA VMR to CRD was expressed as % of the pre-WA response to 2 ml distension, and the area under the volume / %VMR curve was calculated. $P<0.05$ is considered statistically significant (pre-WA vs post-WA, Wilcoxon signed rank test).The results were as follows: 4 MS female rats yielded 12 non-separated male pups. Nine of these pups became hypersensitive to CRD after WA (AUC>71). As a group, the post-WA AUC was significantly increased compared to pre WA (fig 1,*$P=0.004$), indicating visceral hypersensitivity to CRD. The male offspring (n=6) of the NH females did not develop visceral hypersensitivity after WA. In conclusion, we showed that the NH offspring of MS, but not of NH female rats, develops visceral hypersensitivity to CRD after WA later in life. These data suggest that the feature to develop stress-induced visceral hypersensitivity is transferred in a non-genomic behavioral fashion. At present, cross fostering experiments are being carried out to further confirm this hypothesis.

Increased Visceroperception in Patients with Ulcerative Colitis in Remission is related to Mucosal Mast Cell Quantity

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A considerable subset (20%) of patients with ulcerative colitis in remission (UC-R) experience symptoms that resemble Irritable Bowel Syndrome (IBS). Increased visceroperception is a hallmark of IBS. Little is known, however, about visceroperception in patients with UC-R. Mast cells are major suppliers of inflammatory mediators and mast cell count is significantly higher in the colonic mucosa of patients with IBS as compared to controls. Therefore increased visceroperception may be associated with mast cell quantity. Whether an increased mast cell count is also present in colorectal mucosa in patients with UC-R is not known. Our aim was to investigate visceroperception and mast cell counts in the colorectal mucosa of UC-R and healthy volunteers.Nineteen patients with UC-R (9F; 50±3 yrs) and 17 healthy controls (8F; 43±3 yrs) were enrolled. Rectal perception was studied using a barostat assembly, following a ramp distension protocol (0-40 mmHg). Perception of urge and pain was scored on a Visual Analogue Scale (0-100 mm). Colonoscopies were performed with biopsies taken from rectal and colonic mucosa. Mucosal mast cells were identified immunohistochemically (tryptase) and quantified per 100 crypts. Perception of urge at the highest rectal pressures (32-40 mmHg) was significantly increased in UC-R versus healthy controls (70±4 mm vs. 54±7 mm; $p<0.05$). Pain perception in the same pressure range was also increased in UC-R (20±6 mm vs 12±6 mm in healthy controls), but not significantly. The number of mucosal mast cells in the rectum was significantly higher in UC-R than in controls (228±20 cells/100 crypts vs. 163±18 cells/100 crypts; $p<0.05$). Furthermore, a correlation was found between the number of mast cells in the rectal mucosa and perception at the highest rectal pressures ($r=0.39$; $p<0.05$). In colonic mucosa no differences in mast cell profiles were found. Conclusions. In patients with ulcerative colitis in remission: 1) visceroperception to rectal distension is significantly increased 2) mast cell count in rectal mucosa is significantly increased 3) increased visceroperception is correlated with rectal mast cell count 4) increased mucosal mast cell counts may contribute to increased visceroperception in ulcerative colitis in remission.

Intestinal handling during abdominal surgery induces mast cell degranulation and intestinal inflammation in man

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Introduction: Intestinal handling during surgery is increasingly recognized as an important factor involved in the pathogenesis of postoperative ileus (POI). In mice, we previously showed that mast cell degranulation triggered by intestinal handling results in the release of inflammatory mediators and the influx of inflammatory cells leading to POI. To what extent this sequence of events also occurs in man is currently unknown.
Aim: 1. To assess if intestinal handling results in mast cell activation and inflammatory mediator release during abdominal surgery and 2. to evaluate whether intestinal handling leads to intestinal leukocyte recruitment.
Methods: 1. In abdominal hysterectomy patients, peritoneal lavage fluid was obtained during surgery at three different time points: 1. immediately after opening of the peritoneum (basal), 2. after first gentle handling of the intestines (early) and 3. at the end of the surgical procedure, immediately before closure of the abdomen (late). Tryptase, IL1β, IL6, TNFα and IL8 release were determined in the different samples. 2. Another series of patients undergoing an abdominal or a vaginal hysterectomy were invited to have an abdominal ^{99m}Tc-labelled leukocyte SPECT-CT scan 24h before (basal) and after surgery. Clinical recovery (i.e. flatus, defecation and hospital stay) was evaluated in both groups. Results: 1. Gentle intestinal handling resulted in a significant increase of tryptase, but not of the other mediators, in the early samples compared to basal levels (6.4±1.7μg/l vs. 28.4±6.2 μg/l, p=0.02, n=6). In the late samples, tryptase (55.9±12.8μg/l, p=0.002, n=6), IL6 and IL8 were increased (increase compared to basal IL6= 1756±1648 pg/ml, p=0.046 and IL8= 2128±2079 pg/ml, p=0.046, n=6), but not IL1β and TNFα. 2. Leukocyte scanning 24h after surgery showed an increase of intestinal activity compared to basal in abdominal hysterectomy patients (Δ=132.2±8% of preoperative scan, p=0.01, n=8) but not in vaginal hysterectomy patients (Δ = 99.4±12% of preoperative scan, n=8). Clinical recovery was prolonged after abdominal hysterectomy in comparison to vaginal hysterectomy and correlated with the leukocyte activity (r=0.58, p=0.018).
Conclusion: The current study demonstrates that intestinal handling during surgery activates mast cells resulting in the release of inflammatory mediators leading to an influx of inflammatory cells. These results identify mast cells as an important therapeutic target to shorten POI.

Is Cyst(e)ine an Essential Amino Acid in Borderline Preterm Infants? *

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Cyst(e)ine is a non-essential amino acid in adult humans. It can be synthesized from methionine by transsulfuration and this is regulated through the enzyme cystathionase. However, Zlotkin et al reported that cyst(e)ine might be an essential amino acid in preterm infants due to low cystathionase activity (Pediatr Res 1982). No in vivo study has been published to determine if preterm infants are able to convert methionine to cyst(e)ine.To determine the cyst(e)ine requirement in preterm infants with a gestational age of 32 to 34 weeks at the age of 35-37 weeks by use of indicator amino acid oxidation (IAAO) technique.Twenty preterm infants (GA 33 wk ± 1 wk SD and BW 1.73 kg ± 0.30 kg SD) were randomly assigned to one of the graded cystine test diets (11, 22, 32, 43, 65 mg cystine/100 ml formula). After 24 hours of adaptation, cyst(e)ine requirement was determined by using [1-^{13}C]phenylalanine hydroxylation. ^{13}CO2 release from [1-^{13}C]phenylalanine was measured by isotopic ratio mass spectrometry and a two-phase linear regression was used to calculate the cyst(e)ine requirement.Graded dietary intake levels of cystine did not show a decrease in fractional oxidation of [1-^{13}C]phenylalanine. Linear regression of the data showed that the slope was not different from zero (p=0.45) and, therefore, no breakpoint could be calculated.From these data we can conclude that cyst(e)ine is a non-essential amino acid in premature infants with a gestational age of 32-34 weeks. These data do not support the hypothesis that cystathionase activity is limited in premature infants.

The clinical effect of a new infant formula in term infants with constipation: a double-blind, randomized, cross-over trial *

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Infant formula Nutrilon Omneo (New Formula; NF) contains a high concentration of β-palmatic acid (41%) and a mixture of prebiotic galacto- and fructo-oligosaccharides (0.8g/100ml, 90% GOS and 10% FOS). It is hypothesized that NF positively affects stool characteristics in constipated infants. The aim of the study was to investigate the clinical effect of this NF on defecation frequency, stool consistency, painful defecation and fecal impaction in constipated infants.Thirty-eight constipated infants, aged 3-20 weeks, were randomized to NF (n=20) and Standard Formula (SF; n=18) in period 1 and crossed-over after 3 weeks to the other treatment in period 2. Constipation was defined by at least one of the following symptoms: 1) defecation frequency < 3/ week; 2) hard stools; 3) painful defecation; 4) fecal impaction. Primary outcome measures were defecation frequency, stool consistency, painful defecation and presence of fecal impaction. Secondary outcome measures were formula tolerance and weight gain.Period 1 was completed by 35 infants. Defecation frequency increased significantly in both groups: NF from 3.5 - 5.6/week (p=0.005) and SF from 3.5 - 4.9/week (p=0.01), but was not significantly different between the two formulas (CI: -1.11 – 2.60; p= 0.42). Soft stools were found significantly more with NF than SF (53% versus 29%; RR 1.42; CI 0.98-2.06; p= 0.03). No difference was found in painful defecation or the presence of fecal impaction. Twenty-four infants completed period 2. Similarly to period 1, only stool consistency was significantly different between the two formulas (17% had soft stools on NF but hard stools on SF; no infants had soft stools on SF but hard stools on NF, McNemar test p= 0.046). Throughout the study there were no serious adverse effects in either group. Weight gain was similarly on NF and SF; 30 grams / day on NF and 32 grams / day on SF (CI: -11.7 – 6.6; p= 0.57).Conclusion: The addition of high concentration β-palmatic acid and oligosaccharides in NF resulted in softer stools in constipated infants, but not in a difference in defecation frequency. Formula transition to Nutrilon Omneo can be considered as treatment in constipated infants with hard stools.

Effect of Body Position Changes on Postprandial Gastroesophageal Reflux and Gastric Emptying in the Premature Neonate*

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In infants, left side positioning decreases triggering of transient lower esophageal sphincter relaxations (TLESR) and gastroesophageal reflux (GER) but paradoxically delays gastric emptying (GE). The aim of our study was to establish a positioning regimen that would both promote GE and reduce GER by changing body position one hour after feeding. We studied 6 healthy preterm infants (4 male, post menstrual age: 36 (34-38) weeks, weight: 2390 ± 120g) using a combined esophageal impedance and manometry technique. After catheter placement, infants were positioned on the left (LP) or right (RP) side and then gavage fed via an infusion port. After one hour, the infant's position was changed to the opposite side. All infants were studied on two occasions such that position was changed from RP to LP (protocol 1) and from LP to RP (protocol 2) in a cross-over fashion. GE rate was determined with a 13C Na-octanoate breath test. Manometry and impedance tracings were blinded for analysis. Right positioning overall resulted in triggering of more TLESR and liquid GER than left positioning (mean: 3.3±2.2 vs 1.9±1.5 ($p=0.004$) and 4.8±3.4 vs 0.8±1.3 ($p=0.003$) per hour respectively), but less gas GER (0.3±0.7 vs 1.3±1.05, $p=0.04$). The number of TLESR and liquid GER episodes per hour was significantly reduced after position change in protocol 1 (RP 3.7±2.2 / LP 1.7±1.7 ($p<0.001$) and RP 6.0±3.7 / LP 0.2±0.4 ($p=0.013$) respectively), while there was no change after position change in protocol 2 (LP 2.2±1.5 / RP 3.0±2.4 ($p=0.289$) and LP1.5±1.5 / RP 3.5±2.7 ($p=0.067$) respectively). The total number of all GER episodes did not differ between the two protocols however protocol 1 significantly reduced TLESR and liquid GER in the second hour after feeding. GE was faster during protocol 1 than 2 (34.1±11.1 vs 52.9±7.7, $p=0.026$). The GE rate for protocol 1 was similar to premature infants previously studied in the RP only ($p=0.89$) and GE rate for protocol 2 was faster ($p<0.001$) than infants previously studied in the LP only.CONCLUSIONS: A postural strategy of right positioning for the first postprandial hour with a position change to left afterwards promotes GE while at the same time reduces liquid GER in the late post-prandial period when liquid reflux of pH<4 occurs. Infants with GERD have increased acid GER in association with TLESR and right to left positioning may be a useful and simple therapeutic strategy for promoting GE and reducing acid GER.

Gluten tolerance in coeliac disease patients *

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Aim: To determine if coeliac disease (CD) patients can develop tolerance for gluten. Methods: All 78 patients (20-80 years) known at our hospital with biopsy proven CD for 10 years or more were asked informed consent to participate. Tolerance for gluten was defined as no clinical, immunological or histological signs of CD while the patient was not adhering to a gluten free diet (GFD). Health complaints and food intake were checked by the SF-12 and a food frequency questionnaire and serum IgA-EMA and –tTGA and bone mineral density (BMD) were determined. Patients consuming gluten were offered a small bowel biopsy. Gluten peptides specific T-cell lines (TCL) were isolated from the small bowel biopsy samples. Results: 85% of the patients were included: 22 (33%; mean age 28 y; 13 females) were on a gluten containing diet (GCD) (mean time 19y; 1-32). All the patients on a GCD and 98% of these on a GFD reported health complaints. Osteopenia was present in 6 and 13 patients on a GCD and on a GFD, respectively. 10 patients on a GFD had osteoporosis. We performed 15 small bowel biopsies in the patients on a GCD of whom 5 could be classified as Marsh 0, 5 as Marsh 1 and 5 as Marsh 3. EMA and/or tTGA positivity was found in 0, 0 and 2, HLA-DQ2 and/or DQ8 in 2/4, 2/4 and 3/3 and gluten peptides specific TCL in 0, 0 and 2, respectively. We found 10 patients to be tolerant for gluten. Conclusion: Development of tolerance for gluten is possible in certain patients with CD after many years of gluten consumption. This feature may be associated to specific genetic characteristic of the CD patients, since 4 of the 10 tolerant patients in our study had HLA-DQ types different from those commonly associated to CD. More insight in the mechanisms involved in the induction of tolerance is needed to be able to distinguish these CD patients as they would not necessary have to be treated with a life-long GFD.

Cladribine therapy in refractory celiac disease with aberrant T-cells

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AbstractRefractory Celiac Disease (RCD) may be subdivided into RCD type I and type II with phenotypically normal and immature intraepithelial T-cell population respectively. In RCD type II transition into Enteropathy Associated T-cell Lymphoma (EATL) is frequently seen. We have evaluated the effect of cladribine (2-CdA), a cytotoxic purine analogue inducing T-cell depletion , on clinical, histopathological and immunological parameters as well as the toxicity and side effects in a group of RCD II patients.Between 2000 and 2005, 17 patients were included (8 Males/9 Females). All patients had a clonal rearrangement of the TCRg gene and immunophenotyping showed an immature monoclonal T-cell population lacking surface expression of CD3,CD8 and TCR-$\alpha\beta$, in the presence of expression of surface CD103 and intracytoplasmic CD3. Treatment consisted of 2-CdA (0,1 mg/kg/day) intravenously for 5 days, given in 1-3 courses every 6 months depending on the response. All patients tolerated 2-CdA without serious side effects. Six of 17 patients (35.8%) showed a clinical improvement (weight gain, improvement of diarrhoea and hypoalbuminaemia). In 10 patient (58.8%) a significant improvement of the histological status and in 6 patient (35.2%) a significant decrease in immature T-cell percentages was seen. Seven patients (41.1%) developed EATL and died subsequently. One patient died from progressive refractory state with emaciation. Conclusions: 2-CdA-treatment in RCD type II is feasible, well tolerated and can induce improvement of clinical and histological parameters as well as a significant decrease of immature T-cell percentages in a subgroup of patients, albeit does not prevent EATL-development.

Intestinal Fatty Acid Binding Protein: The role of the gut in the early phase of sepsis

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Following major surgery, the development of sepsis and multiple organ failure (MOF) are important determinant factors of the outcome. Splanchnic hypoperfusion and resulting intestinal damage have been widely implicated as central events in the development of sepsis and MOF in high-risk surgical patients.The aim of the study was to evaluate the relation between intestinal damage, intramucosal perfusion, and mortality in high-risk surgical patients with an early phase of sepsis.Two groups of patients were selected: patients that developed abdominal sepsis, who were characterized by peritonitis resulting from a perforation in the gastrointestinal tract (n=19); and patients with non-surgical sepsis caused by pneumonia (n=9). Patients were included in the study during the first 24 hours after admission to the ICU and followed during their stay in the ICU. Circulating Intestinal Fatty Acid Binding Protein (I-FABP), a small cytosolic protein constitutively present in mature enterocytes, was used as a marker for intestinal mucosal cellular damage. Intramucosal perfusion was assessed by gastric tonometry (PiCO2, and mucosal-arterial pCO2 gap (Pr-aCO2 gap)). On day 28, outcome was determined by classification of patients as survivor or non-survivor.The highest plasma levels of I-FABP were measured directly after ICU admission. At that time, non-survivors had significantly higher I-FABP values than survivors (507.7 vs 137.6 pg/ml, $p<0.04$). Interestingly, especially high-risk surgical patients with abdominal sepsis were responsible for high admission I-FABP levels in non-survivors (673.2 vs 259.5 pg/ml, $p<0.04$). Circulating I-FABP correlated strongly with Pr-aCO2 gap (Pearson's $r2=0.56$, $p<0.001$) in all patients and gastric mucosal PiCO2 ($r2=0.57$, $p=0.001$) in patients with abdominal sepsis. In conclusion, this study shows that splanchnic hypoperfusion correlates strongly with intestinal mucosal damage and that elevated plasma I-FABP levels correlate with a poor outcome in high-risk surgical patients with abdominal sepsis. The results of this study support the hypothesis that splanchnic hypoperfusion contributes to intestinal mucosal damage associated with the development of sepsis following major surgery.

The clinical significance of plasma arginase-1 during liver surgery; effects of hepatocyte injury on arginase-1 release and plasma arginine levels in man.

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Low arginine (ARG) plasma levels are a common finding after major abdominal surgery. Since ARG is involved in nitric oxide synthesis, T-cell activation and collagen synthesis, ARG deficiency may compromise endothelial function, immune function, wound healing and hence postoperative recovery. The enzyme arginase-1, abundantly present in hepatocytes, catalyzes the conversion of ARG to ornithine (ORN) and urea. Hepatocyte injury leads to arginase-1 release, which may result in extracellular ARG breakdown. We recently showed that liver manipulation during surgery induces significant hepatocyte injury and now hypothesized that this leads to increased arginase-1 plasma levels and accelerated ARG breakdown.
Sixteen patients undergoing partial hepatectomy were studied. Blood was sampled preoperatively and during liver manipulation. Arginase-1 plasma levels were measured by ELISA, ARG and ORN levels by HPLC. From 6 patients plasma and whole blood samples were incubated for 40 min at 37˚C to assess arginase activity in vitro. Changes in ARG and ORN plasma levels were measured and arginase activity was expressed as the amount of ORN formed per minute.
In line with our hypothesis, mean (SEM) arginase-1 plasma levels increased during liver manipulation from 17.8 (4.1) ng/ml (low arginase) to 133 (30) ng/ml (high arginase), (p=0.002). However, plasma concentrations of ARG and ORN remained unchanged (p=0.3 and p=0.2 respectively). In accordance with these in vivo findings, no significant changes in ARG and ORN levels occurred when plasma samples with increased arginase-1 levels were incubated at 37˚C for 40 min (low arginase: [ORN] +0.13 (0.09) µM/min (p=0.2 vs. zero); high arginase: [ORN] +0.23 (0.20) µM/min (p=0.3 vs. zero)). When whole blood samples were incubated similarly, a significant decrease of ARG plasma levels with a stoichiometric increase of ORN levels was found (low arginase: [ORN] +0.93 (0.19) µM/min (p=0.005 vs. zero); high arginase: [ORN] +0.95 (0.34) µM/min (p=0.04 vs. zero)). These changes were independent of arginase-1 plasma levels (p=0.9; low arginase vs. high arginase) and can be explained by ARG uptake and arginase activity by intact erythrocytes.
Conclusion. Hepatocellular injury by liver manipulation leads to arginase-1 release resulting in increased arginase-1 plasma levels. Surprisingly, this does not stimulate extracellular arginine breakdown, which sheds new light on earlier reported arginine lowering properties of circulating arginase-1.

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Decreased circulating arginine in ALF mice does not compromise whole body NO production

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In fulminant hepatic encephalopathy (HE), the plasma level of the precursor of nitric oxide (NO) Arginine is reduced. In contrast, nitric oxide (NO) production, measured as plasma NOx is increased. This contradiction could be due to failure of plasma NOx to represent NO production. Therefore, we studied whole body (Wb) ARG (precursor of NO) and NO metabolism using stable isotope technology in a newly developed acetaminophen (APAP) induced acute liver failure (ALF) mouse model with pre-coma HE after 20h.Method: In post absorptive C57Bl6/J mice, an oral dose of 200+200 mg/kg of APAP or drinking water (control) was given at t=0+1 h. At T=20 h, Wb ARG and Arginine to NO and Urea/Ornithine conversion was measured in carotid artery/jugular vein catherized mice under anaesthesia using a primed-continuous infusion of 15N-CIT,15N2-2H2-ARG and 13C-UREA stable isotopes. At plasma steady state, arterial (art) plasma was collected. Whole body rate of appearance (WbRa), NO production, de novo ARG and rate of urea converted from ARG (ARG-UREA) were calculated. Statistics: t-test, sign $p<0.05$, data as mean ± SEM. Results: Twelve of the 17 APAP animals had ALT>1000 IU/l (ALF group) and showed behaviour changes at a level of pre coma. Art ARG was decreased in the ALF group (65 ± 15 vs. 134 ± 6 µM). Art ORN (190 ± 19 vs. 84 ± 7 µM) and ARG-UREA conversion (19 ± 3 vs. 13 ± 1 nmol/10 gr bw/min) were increased. WbRa of ARG, Wb NO production and de novo ARG were unchanged compared to control animals.Conclusion: Reduced plasma ARG is probably caused by release of the enzyme arginase from the injured liver and subsequent ARG to ORN/UREA conversion. Reduced Arginine availablity, however, did not affect NO production at this early stage of HE.

Glutamine Is An Important Precursor For De Novo Synthesis Of Arginine In Man

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Normalisation of depressed plasma concentrations of glutamine (Gln) and arginine (Arg) is associated with better clinical outcome. Supplementing Gln may be a way to provide the patient with Gln as well as Arg, since it has been suggested that citrulline (Cit), a product of intestinal Gln metabolism, can be taken up by the kidney to serve as a precursor for *de novo* Arg synthesis. However, this pathway has never been described conclusively in man. Aim of this study was to quantify the metabolic pathway from Gln to Cit and then to Arg in humans.
Eight patients undergoing major upper GI surgery were included in this study. Before surgery, a catheter was placed in an antecubital vein for stable isotope infusion. During surgery a primed and constant infusion of L-[2-^{15}N]-Gln, L-[ureido-^{13}C-$^{2}H_2$]-Cit and L-[guanidino-$^{15}N_2$]-Arg was started and continued for 2.5 h. Blood samples were drawn from an arterial line before the start of the infusion and every 30 minutes thereafter. Enrichments of Gln, Cit and Arg, measured with liquid chromatography - mass spectrometry, were used to calculate the turnover of these amino acids and the conversions from Gln into Cit and Cit into Arg. Results are expressed in mean ± SEM. Isotopic steady state was achieved within 30 minutes for all infused stable isotopes (cTTR ^{15}N-Gln: 6.45 ± 0.29%, p<0.001 vs. baseline). At steady state significant enrichments were observed of ^{15}N-Cit and ^{15}N-Arg (cTTR: 5.65 ± 0.38% and 1.35 ± 0.07% respectively, p<0.001 vs. baseline). Whole body turnover rates of Gln, Cit and Arg were 328 ± 15, 11 ± 1 and 44 ± 2 µmol/kg/h, respectively. Whole body *de novo* Cit production derived from Gln was 9.8 ± 1.0 µmol/kg/h, representing about 89% of total Cit turnover. *De novo* Arg production from Cit was 9.4 ± 0.7 µmol/kg/h, which represents about 20% of total Arg turnover and 85% of the total Cit turnover. The calculated contribution of Gln to Arg *de novo* synthesis was 76% (85% x 89%).
Conclusion: This is the first study that proves the quantitative importance of the metabolic relationship between Gln turnover and *de novo* Arg synthesis in humans. Gln is a precursor for 76% of *de novo* synthesized Arg. Our next step will be to quantify the contribution of the intestines and the kidneys to this pathway.

Significant liver damage in patients with bleeding disorders and chronic hepatitis C: non-invasive assessment of liver fibrosis using transient elastography (Fibroscan®)

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Most patients with bleeding disorders treated before 1992 with clotting factor products have been infected with hepatitis C virus (HCV), predominantly with genotype 1. Current antiviral therapy leads to sustained virological response in only 50% of these patients. Also, hepatitis C is generally thought to have a relatively benign course in this patient category. Liver biopsy is generally not performed because of increased bleeding risk and high costs of blood clotting products. We therefore assessed liver fibrosis and cirrhosis non-invasively by using liver stiffness measurement (LSM). Methods: We enrolled 124 consecutive consenting patients with bleeding disorders (95% males with hemophilia) and chronic hepatitis C (mean age 42 (range 16-86) yrs, BMI 24 (18-41) kg/m2, 90% HCV genotype 1 with infection duration 34 (14-40) yrs, 9% HIV coinfected, 2% HBV coinfected). Liver fibrosis and cirrhosis were assessed by LSM using Fibroscan® with the following cut-offs: F0/F1<7.1 kPa: F2 7.1-9.5 kPa: F3 9.6-12.5 kPa: F4>12.5 kPa. For validation of Fibroscan® outcome results of LSM were compared with concomittant liver biopsy (Metavir score) in 54 additional hepatitis C patients without bleeding disorders: for F0/F1 vs F2 or higher: sens. 79%: spec. 83%: PPV 79%: NPV 83% AUROC 0.88. For distinguishing > F3 vs lower values, results were similar. Results: F0/F1 was present in 40%, F2 in 26%, F3 in 18%, F4 in 17% of the patients with clotting disorders. 65 percent of patients with a Fibroscan®-based diagnosis of cirrhosis, would not have been diagnosed on the basis of laboratory and ultrasonographic findings. Older age at infection, high BMI, male sex and HBV or HIV coinfection were independent risk factors for fibrosis. Conclusions: In patients with bleeding disorders and hepatitis C, prevalence of severe fibrosis/cirrhosis 34 years after infection detected by Fibroscan® was high, with significant impact on patient management. Ca. 60% of the patients had fibrosis grade F2 or more; these patients are in need for antiviral therapy.

Liver injury in long-term Methotrexate treatment in psoriasis is relatively infrequent.

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Background: Methotrexate (MTX)-induced liver damage in psoriasis patients has led to dermatologic guidelines that stipulate monitoring of liver injury by means of serial liver biopsies. Recent literature suggests that MTX might be significantly less hepatotoxic as previously assumed, which calls for reconsideration of the routine use of liver biopsies.Aim: An evaluation of prevalence and development of liver injury in patients with psoriasis on long-term MTX treatment.Methods: Retrospective chart review (1976-2005) was performed to obtain information about demographics, details of MTX treatment and histology (Roenigk classification), presence of risk factors and liver enzyme test results. Information was collected using a structured database.Results: 125 patients (F58/M67; mean age 45.0, SD 12.7 yrs) received a median cumulative MTX dosis of 2113 mg (range 180-20235) over a period of 228 weeks (range 16-1763). We analyzed 279 liver biopsies, and 71% were classified as Roenigk grade I, 14% as Roenigk grade II, 12% grade IIIa, 2% grade IIIB and 2% grade IV.Cumulative dose, weekly prescribed dose, age, duration of treatment were not associated with development of liver injury. Elevated gamma glutamyl transferase levels predicted the presence of liver injury (Odds ratio 1.80; 95% CI 1.30-2.49). A total of 68 patients had multiple biopsies. Three percent improved, 72% did not change and in 25% liver histology deteriorated. The majority of cases (67/80; 84%) that progressed to Roenigk 2 had a cumulative dose of less than 6000 mg, while there was no further liver injury in those who continued MTX. Conclusion: MTX related liver injury is less frequent than previously thought. Liver injury was unrelated to MTX dose and duration, but in cases with liver injury it occurred at cumulative doses of less than 6000 mg.

Aberrant staining of hepatocystin in polycystic liver disease

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Polycystic liver disease (PCLD) is a rare, autosomal dominant inherited condition in which numerous cysts develop scattered throughout the liver. The cysts arise from overgrowth and subsequent dilation of intralobular bile ductules. PCLD is associated with mutations in PRKCSH and SEC63, respectively encoding hepatocystin and SEC63p. Hepatocystin is the catalytic β-subunit from glucosidase II α, which is thought to be involved in folding and quality control of glycoproteins in the endoplasmic reticulum (ER). In yeast SEC63p is involved in posttranslational protein translocation and ER associated degradation. The objective of this study was to assess the cellular localization of hepatocystin and SEC63p in normal and PCLD liver tissue, as well as in various cell lines.

The localization of hepatocystin and SEC63p in HELA, HepG2 (human hepatocytes) and SK-ChA-1 (human cholangiocytes) cell lines as well as in frozen sections of normal and PCLD liver tissue was examined using immunofluorescence microscopy. The proteins were stained with commercially available antibodies and appropriate fluorochrome labelled secondary antibodies.

Hepatocystin staining was compatible with an ER like pattern in all tested cell lines, while SEC63p revealed granular staining with overlap in staining pattern with hepatocystin. In normal liver tissue hepatocystin and SEC63p localized to hepatocytes and to the apical side of bile ducts. SEC63p bile duct staining was very intense. In PCLD tissue from a PRKCSH 1338-2A>G mutation carrier hepatocystin staining was absent from epithelial lining of the cyst wall, which contrasted with positive staining of the hepatocytes from the same sample. In addition, SEC63p staining was present in hepatocytes, and very pronounced in cyst wall epithelium.

In conclusion: The staining pattern of hepatocystin and SEC63p overlap in various cell lines and normal liver tissue. SEC63p preferentially localizes to the bile duct whereas hepatocystin stains bile ducts and hepatocytes in equal intensity. In PCLD tissues, hepatocystin staining is conspicuously absent from the cyst epithelial lining, which may favour a second hit theory.

First in vitro comparison of two bioartificial liver support systems: MELS CellModule and AMC-BAL.

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Bioartificial liver support (BLS) systems are developed to bridge acute liver failure patients to liver transplantation. Clinically applied BLS systems are difficult to compare in terms of overall hepatocyte-specific function and their effect on clinical outcome. Particularly, the large variability in cell type and isolate, test set-up, patient population, outcome parameters and differences in data presentation hamper simple device comparison. In this study, two clinically applied BLS systems, the Modular Extracorporeal Liver Support (MELS) CellModule and the AMC-bioartificial liver (AMC-BAL), have been compared in an in vitro set-up.Ten billion of freshly isolated porcine hepatocytes were loaded in the MELS and the AMC-BAL (n=5) and cultured for seven days at 37oC in the same culture medium. The overall in vitro functionality of both bioreactors was assessed at day 1, 2, 4, and 7. Hepatocyte-specific functions (ammonia and lidocaine elimination, urea and albumin production), hepatocellular cell damage (LDH and AST release) and general metabolic activity (oxygen and glucose consumption, and lactate production) were determined during a four hour test period.In general, both bioreactors functioned well with an average decrease of 9.7% in the hepatocyte-specific functions over 7 days. Lidocaine elimination at day 1 and 2 was significantly higher in the AMC-BAL. In addition, ammonia elimination showed a significant higher trend for the AMC-BAL over 7 days. All other parameters at all days did not differ between both bioreactors. Despite these observations, some trends were observed: glucose consumption and lactate production were lower in the MELS at day 4 and 7, whereas AST and LDH release were higher at day 1 in the AMC-BAL.In conclusion, this first in vitro comparison of two clinically applied BLS systems (MELS CellModule and AMC-BAL) shows comparable functional capacity over a period of seven days.

Endoscopic Treatment of Esophagogastric Variceal Bleeding in Patients with Non-cirrhotic Extrahepatic Portal Vein Thrombosis: A Long-term Follow-up Study.

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Esophagogastric variceal bleeding is the most important complication of extrahepatic portal vein thrombosis (EPVT), and is usually treated endoscopically. Little is known on the prognosis of these patients. In the current cohort study we investigated the clinical outcome and efficacy of endoscopic treatment in patients with variceal bleeding secondary to EPVT.Consecutive patients with variceal bleeding secondary to non-cirrhotic, non-malignant EPVT, who underwent endoscopic treatment at our hospital between 1982 and 2005, were enrolled in this study. Data on diagnosis, endoscopic procedures and outcome were collected by systematic chart review. Overall and re-bleeding-free survival was calculated by the Kaplan Meier method. Multivariate Cox regression, stratified for number of re-bleedings, was used to determine predictors of re-bleeding.Thirty-one patients (29% males; median age 45.6 years (range 3.5–87.5)) were followed after their first bleeding episode (median follow-up 8.3 years, range 0-22.4). Underlying diseases were protein S deficiency (n=5), infections (n=3), IBD (n=1) and other forms of hypercoagulability (n=10). A total of 164 endoscopic procedures were performed, including variceal ligation (n=36), sclerotherapy (n=125) or both (n=3). In all patients, initial control of bleeding was obtained. Re-bleeding occurred in 13/31 (42%) patients; in 10 (77%) after sclerotherapy, in 1 (8%) after band ligation and in 2 (15%) after both modalities. Overall re-bleeding risk was 19% (95% CI 9-30) at 1- and 43% (95% CI 29-59) at 5-years. Extension of thrombosis appeared the only independent predictor of re-bleeding, with a nearly 3-fold risk for EPVT patients with concomitant splenic and/or mesenteric vein thrombosis (RR=2.93;P=0.03). Two complications, both sclerotherapy-induced, were noted: esophageal stenosis needing dilatation, and ulcer bleeding leading to death. A porto-systemic shunt procedure was performed in 6 patients, in 5 for variceal (re)bleeding and in 1 for refractory ascites. Seven patients died, 6 due to the underlying disease causing EPVT and 1 after bleeding. Overall 5- and 10-year survival was 100% and 65 % (95% CI 42%-91%), respectively.In patients with variceal bleeding from EPVT, endoscopic procedures, in particular band ligation, appear safe and effective with low re-bleeding risk. Bleeding related mortality is rare; survival appears primarily determined by the underlying disease causing EPVT.

Does MELD Predict Survival in Budd-Chiari Syndrome?

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An adequate prognostic model for Budd-Chiari Syndrome (BCS) is as yet not available. The recently developed 'Rotterdam BCS index', including encephalopathy, ascites, prothrombin time and bilirubin, is limited by a categorical design. MELD, including creatinine, bilirubin and INR, is a widely accepted, objective and continuous scoring system for chronic liver disease, but has never been evaluated in BCS. Our aim was to assess the accuracy of MELD in prognostication of BCS. Patients, diagnosed with non-malignant BCS between 1984-2001 (n=237), were derived from a large international study. Hospitalised patients (n=281) with End-Stage Liver Disease (ESLD) were used to compare MELD in BCS to MELD in other chronic liver diseases. MELD and Rotterdam BCS index were assessed according to the currently used equations. Kaplan Meier and Cox regression methods were used to analyse survival. Receiver Operating Characteristic (ROC) curves and concordance (c)-statistics were employed to assess a model's ability to predict 1-year mortality. Correlation was analysed by Pearson's coefficient. Median MELD score at baseline was 12.5 (range –7.4 to 43.4) for BCS and 11.3 (-3.0-49.5) for ESLD (P=0.12). C-statistic of MELD in BCS was 0.70 (95% CI 0.59-0.80), as opposed to 0.85 (95% 0.80-0.90) in ESLD. Prognosis was significantly poorer in ESLD with 5-year survival of 44% (95% CI 35-52) versus 69% (95% CI 62-76) in BCS (P<0.001). Median Rotterdam score in BCS was 1.16 (range 0.02-4.03) and the C-statistic was 0.76 (95% 0.67-0.85). Correlation between MELD and Rotterdam BCS index was 0.61 and most of the discrepancy existed in patients with ascites and/or encephalopathy but otherwise preserved liver function. Hence, a new model was created by multivariate Cox analysis with MELD and clinical parameters, and the equation was as follows: MELD + 16*ascites + 17*encephalopathy. Both ascites as encephalopathy were scored as present (1) or absent (0). The C-statistic of this model was 0.75 (95% CI 0.65-0.85).

In conclusion, MELD showed a reasonable, yet poorer discriminative ability in BCS than in ESLD. This is primarily explained by a heterogeneous clinical course and hence variable prognosis of BCS. Complications of portal hypertension are probably more important for the prognosis of BCS than ESLD. Therefore, a new model including both MELD and important clinical parameters combines good discriminative ability with clinical usefulness, and may be used to predict survival in

Ursodeoxycholic acid exerts no beneficial effects in gallstone patients awaiting cholecystectomy: a randomized, double-blind, placebo-controlled trial.

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Although treatment with ursodeoxycholic acid (UDCA) and impaired gallbladder contraction have been claimed to reduce risk of biliary pain and acute cholecystitis in gallstone patients, prospective data are lacking. In a randomized, double-blind, placebo-controlled trial, we investigated effects of UDCA (750 mg a.n.) on biliary colics and complications in 177 symptomatic gallstone patients scheduled for elective cholecystectomy performed after 92±4 days [median and range: 77; 4-365]). Also, colics after cholecystectomy were scored during 6 months. Patients were stratified for colic nr. in the previous year (< 3: 32 pts; ≥ 3: 145 pts). Baseline ultrasonographic gallbladder motility studies were performed in 126 consenting patients, indicating that 54 patients were strong contractors (minimal gallbladder volume ≤ 6 mL) and 72 patients were weak contractors (> 6 mL). We found that only 23 patients (26%) receiving UDCA and 29 (33%) receiving placebo remained colic-free (P = 0.3). Also, actuarial analysis of the colic-free interval did not reveal any difference between both groups. In the placebo group there were 3 pre-operative complications (pancreatitis, cholecystitis, choledocholithiasis), and 2 post-cholecystectomy complications (pancreatitis, choledocholithiasis). In contrast, all 4 complications in the UDCA group occurred after cholecystectomy (pancreatitis (N=3), choledocholithiasis, P = 0.16). Nr. of colics, non-severe biliary pain, analgesics intake and nr. of patients with post-cholecystectomy colics (14% vs 7%, P = 0.2) were comparable in both groups. Likelihood to remain colic-free was comparable in strong and weak contractors (31% vs 33%, P = 0.8). In weak contractors, UDCA appeared to decrease likelihood to remain colic-free (21% vs 47% in the placebo group, P = 0.02). Patients with low nr. of colics prior to the study were more likely to remain colic-free (59% vs 23% in pts with high nr. of prior colics, P < 0.001).
Conclusion: Ursodeoxycholic acid does not reduce biliary colics in patients awaiting cholecystectomy.

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Chronic renal failure after liver transplantation

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The incidence of chronic renal failure (CRF) at 5 years after liver transplantation (LTX) is reported to be 18,1% in the USA (Ojo et al, NEJM Sept 2003). Our aim was to evaluate the long-term renal function after LTX in our center.
We used our LTX database to retrieve the glomerular filtration rate (GFR). GFR was calculated before LTX, and at 1-, 2-, 5-, 10-, and 15 years using the Modification of Diet in Renal Disease study (MDRD) equation comparable to the Ojo study. CRF was defined as a GFR $\leq$ 29 mL/min/1,73 m2 or the development of end stage renal disease for which either dialysis or kidney transplantation was performed. Moderate renal failure (GFR 30-60 mL/min/1,73m2) was also evaluated. From April 1979 to March 2004, 677 patients underwent LTX. We included only adults (age > 18), primary LTX, and only those who survived the first three post-operative months. We excluded those with CRF prior to LTX and those who had LTX combined with any other organ. The remaining group consisted of 414 patients; 217 females and 197 males. The age at LTX varied from 18 to 66 with a median value of 45. The indications for LTX were alcoholic cirrhosis (16%), cholestatic liver disease (34%), cryptogenic cirrhosis (10%), hep C (6%), hep B (7%), acute liver failure (6%), and various other reasons (21%). The immune suppression given in our center can be divided in three period's; calcineurin inhibitor free period (1979- 1984), mainly cyclosporin based triple therapy (1984 – 1993) and CsA or FK506 based double or triple therapy (after 1993).
The median (interquartile range) values of estimated GFR at LTX date, 1-, 2-, 5-, 10-, and 15 years were 85,0 (45,1), 66,6 (29,4), 65,3 (27,1), 68,9 (23,8), 67,6 (23,5) and 66,2 (22,5) respectively.
The cumulative percentages of patients with a GFR $\leq$ 29mL/min/1,73 m2 at 1-, 2-, 5-, 10- and 15 years were 1,0%, 1,9%, 3,8%, 5,9%, and 5,9% respectively. The percentages of patients with a GFR between 30 and 60 mL/min/1,73 m2 at 1-, 2-, 5-, 10-, and 15 years were 35,9%, 38,4%, 26,9%, 27,5% and 30 % respectively. We found no relation between the type of immunosuppression and the incidence of GFR $\leq$ 29 mL/min/1,73 m2. Conclusion: In contrast to 18,1% CRF after 5 years found in the Ojo study, we found 3,8% CRF after 5 years using a large cohort of patients after LTX with a long follow-up. Contributing factors for this difference could be; Low Hep C incidences in our LTX program, long intensive follow up in our own center.

Inflammatory bowel disease after liver transplantation: risk factors for recurrence and de novo disease.

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Inflammatory bowel disease (IBD) is associated with primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH) and can recur or develop de novo after liver transplantation (OLT). The aim of this study was to investigate the incidence and severity of inflammatory bowel disease after liver transplantation and to perform an analysis for possible risk factors. Ninety-one patients transplanted for PSC or AIH, without prior colectomy, were included. Sixty patients were transplanted for PSC, 31 for AIH. Inflammatory bowel disease activity before and after OLT were studied, and possible risk factors for recurrence or de novo disease analyzed in a multivariate model. Forty-nine patients (54%) had IBD before OLT, mainly ulcerative colitis. Forty patients (44%) had active IBD after transplantation: recurrence in 32 and de novo in 8 patients. Cumulative risk for IBD after OLT was 15, 39 and 54 % after 1, 5 and 10 years, respectively. In 59% of the patients with IBD prior to OLT the disease was more active after transplantation. Risk factors for recurrent disease were: symptoms at time of OLT, short interval between diagnosis of IBD and time of OLT and use of tacrolimus after transplantation. 5-aminosalicylates were protective. A cytomegalovirus (CMV) positive donor/negative recipient combination increased the risk for de novo IBD. Possible explanations for the increase in IBD seen in patients using tacrolimus are a decrease in regulatory T-cells, diminished apoptosis of T-cells, and an increase in intestinal permeability in patients using this drug. CMV infection could contribute to IBD-pathogenesis by influencing endothelial VCAM-1 expression, mucosal interleukin-6 production, and increasing intestinal permeability.
Conclusions: 1. Recurrent and de novo IBD are common in patients transplanted for PSC or AIH 2. In patients with previous IBD the disease runs a more active course compared to pre-transplantation 3. Risk factors for recurrence are: symptoms at time of OLT, short interval between diagnosis of IBD and time of OLT and use of tacrolimus. 4. Risk factor for de novo disease is: a cytomegalovirus (CMV) positive donor/negative recipient combination

Hepatotoxicity of long-term and low-dose 6-thioguanine in IBD patients

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Introduction: Initial data on short-term efficacy and toxicity of 6-thioguanine (6-TG) in IBD-patients who were intolerant or refractory to azathioprine (AZA) or 6-mercaptopurine (6-MP) were promising, however these have been challenged by recent reports concerning its potential hepatotoxic effect (nodular regenerative hyperplasia (NRH) and veno-occlusive disease (VOD)). Nonetheless, the hepatotoxicity of 6-TG may be a dose-dependent phenomenon. Aims & MethodsIn the Netherlands 6-TG therapy was generally initiated in a standard dosage of 20 mg/day, which is significantly lower than reported dosages in literature (40 to 80 mg/day). We conducted a study in IBD-patients treated with 6-TG for at least 30 successive months to evaluate liver histology, its relationship with 6-TG use, laboratory parameters (including 6-TGN measurements and TPMT genotyping), and abdominal ultrasonography.
Results: Thirty patients (F:13/M:17 and CD:17/UC:13) underwent a liver biopsy after using 6-TG (median dosage 20 mg) for a mean period of 39 months (range 30-53 months). 6-TG therapy was initiated due to intolerance to AZA/6-MP (N=26), de novo (N=3) and refractory to AZA/6-MP (N=1). No clinically relevant changes in liver tests and whole blood counts (no thrombocytopenia) were observed over time. The mean 6-TGN level was 580 pmol/8x108 RBC (SD 296, range 106-1199). TPMT genotyping (N=21) revealed only one patient with a mutant TPMT allele (6-TGN: 1092 pmol/8x1 RBC). Ultrasonography showed two cases of steatosis (7%), but no splenomegaly. The mean cumulative dose of 6-TG was 22645 mg (range 12150-44400 mg). Histological evaluation revealed: no abnormalities (N=15, 50%), slight regenerative changes (N=7, 23%), slight steatosis (N=3, 10%), slight fibrosis (N=2, 7% (1 x alcohol abuse)), suspicion of VOD (N=1, 3%), steatosis+mild fibrosis (N=1, 3% (apparently NASH)) and primary sclerosing cholangitis+hemochromatosis (N=1, 3%). No cases of NRH were detected. The 6-TGN level, cumulative dose and TPMT status were not correlated with pathohistological findings. ConclusionIn the majority of this cohort of IBD-patients, long-term use of low-dose 6-TG (20 mg/day) did not induce clinically relevant histological liver abnormalities. Hepatotoxicity due to 6-TG use may indeed be dependent on the dosage of 6-TG. Nonetheless, rigorous and frequent monitoring (including a liver biopsy) of IBD patients using low-dose 6-TG as a rescue drug remains mandatory.

Nodular regenerative hyperplasia and sinusoidal dilatation of the liver in a non-thiopurine using IBD-cohort

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Introduction: The use of thiopurines (azathioprine, 6-mercaptopurine and 6-thioguanine) has been associated with the induction of nodular regenerative hyperplasia (NRH) and sinusoidal dilatation (SD) of the liver in IBD patients. However, it is unclear whether IBD itself is not a risk factor in inducing these histological liver abnormalities.
Aims & Methods: Between 1980 and 2005 liver histology was obtained from IBD patients, independent of laboratory results or clinical signs, who underwent gastrointestinal surgery indicated for their IBD. The liver biopsy specimens from patients using thiopurines were excluded in order to asses the prevalence of NRH and SD of the liver in a non-thiopurine using IBD-cohort from a referral centre. The liver specimens (staining: H&E, reticuline and Gomorri trichrome) were evaluated by two blinded liver pathologists. Pathohistological outcomes were related to disease and patient characteristics.
Results: Eighty-five patients (M:37%/F:63% and CD:62%/UC:38%) underwent 92 surgical procedures during which liver tissue (wedge:23%/needle:77%) was obtained. Median age at biopsy was 36 years (range 15-73 years) and median duration of disease was 5 years (range 0-56 years). Severe SD (> 2/3 of the specimen) was observed in 3,3%, moderate SD (1/3 to 2/3 of the specimen) in 8,7%, slight SD (0 to 1/3 of the specimen) in 21,7% and no SD in 66,3% of all biopsies, respectively. A significant difference was observed in type of IBD when considering both severe and moderate SD (combined N=12) as a histological relevant abnormality. Significantly more patients were diagnosed with CD (N=10) compared to UC (N=2) (P=0,022). In addition, there was a significant difference in gender as relatively more patients, with at least moderate SD, were male (P=0,012). One liver specimen was excluded for evaluation on NRH as it was not properly stained. Nodular regenerative hyperplasia was detected in 5,5% of biopsies (M:2 (2xCD) and F:3 (1xCD)). The age at biopsy was significantly correlated with NRH (r=-0,256, P=0,014).
Conclusion: Nodular regenerative hyperplasia (5,5%) and sinusoidal dilatation of the liver (13% (at least moderate)) were relatively common pathohistological findings in our non-thiopurine using IBD-cohort. The reported association between thiopurine use and NRH and SD should be weighed against the background prevalence of these two histological liver abnormalities in the IBD population.

Assessment of the future remnant liver before partial liver resection: A comparison between liver volume and function measured by hepatobiliary scintigraphy.

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The current guidelines for safe liver resections are based on preoperatively determined morphological volume of the future remnant liver (FRL) by CT volumetry. Safe resection can be performed when the FRL exceeds 30% of total liver volume. However the functional significance of morphological volume in patients with parenchymal liver disease is questionable, and may not represent liver function.Hepatobiliary scintigraphy (HBS) using ^{99m}Tc- mebrofenin, is a non-invasive, quantitative method for evaluating total and regional liver function. Recently,^{99m}Tc -mebrofenin SPECT has been developed for the assessment of functional liver volume, in addition to liver function.The aim of this study was to assess the use of ^{99m}Tc -mebrofenin SPECT for the measurement of liver volume and to compare liver volume with liver function, measured by HBS.Thirteen patients, planned to undergo liver resection, were divided into patients with normal livers (n=6) and compromised livers (n=7, cholestasis, chronic inflammation, steatosis or fibrosis). CT volumetry was performed to determine liver volume(LV). HBS, and SPECT were used to determine liver function(LF) and functional liver volume (LFV), respectively. Preoperatively, total liver function (TLF), total functional liver volume (TLFV) and total liver volume (TLV), as well as estimated FRL function(FRLF), FRL functional volume (FRLFV) and FRL volume(FRLV) were determined. Three days postoperatively, actual remnant liver functional volume (RLFV) was measured with SPECT.There was a positive correlation (r=0,87) between pre-operative FRLFV determined with SPECT, and the actual postoperative RLFV. There was also a correlation (r=0,84) between TLV assessed with CT and TLFV assessed with SPECT. There was no correlation between TLV and TLF, nor between TLFV and TLF. In patients with normal livers, there was a strong correlation between FRLV and FRLF (r=0,98), as well as FRLFV and FRLF (r=0,96). In patients with compromised livers, the correlation between FRLV (r=0,75), FRLFV (r=0,64) and FRL function was not significant.This study indicates that it is feasible to estimate FRL functional volume with ^{99m}Tc -mebrofenin SPECT and that it relates to volume measured with CT. In patients with normal liver parenchyma, CT volumetry correlates with function. However, in patients with compromised livers, CT volumetry of the liver is unreliable and additional functional assessment,such as HBS, is required.

Is the preferred treatment of hepatocellular adenoma conservative or surgical?

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The diagnosis of hepatocellular adenoma can significantly impact on the lives of, often, young females. Adenomas are associated with the risk of rupture and malignant degeneration. Controversy exists whether the preferred treatment for hepatocellular adenomas is conservative or surgical. Significant improvements in radiological imaging have enabled better classification of solid liver lesions and frequently allow differentiation of adenomas from other benign and malignant tumours. The aim of the present study was to test a protocol in which adenomas smaller than 5 cm were conservatively treated initially.In our tertiary referral centre we prospectively collected data of 48 consecutive women with a hepatocellular adenoma who visited our hospital from January 2000 until December 2004. Their median age was 36 (range 19-53). All patients were discussed in a weekly multidisciplinary meeting. The protocol for diagnostic work-up consisted of multiphasic MRI or CT and preferred treatment was observation if the adenoma was <5 cm. Median follow-up was 22 months. In sixteen patients (33%) the adenoma was an incidental finding. Forty-five patients (94%) used oral contraceptives. Sixteen patients (33%) presented with a solitary hepatocellular adenoma and thirty-two patients (67%) presented with multiple adenomas. Liver steatosis was significantly more often present in the latter patients than in those with a solitary lesion (59% vs. 19%, P = 0.008). Biopsies were performed elsewhere in 13 patients. Six of these were not conclusive. Invasive procedures (surgery and embolisation) were applied to 14 patients (29%), because of tumour size >5 cm (n=6), malignant characteristics (n=3) or haemorrhage (n=3) or pregnancy wish (n=2). Thirty-four patients (71%) were observed. Haemorrhage and malignant degeneration did not occur. None of conservatively treated lesions showed progress in size after cessation of oral contraceptives use. After initial conservative treatment, 4 patients underwent surgical resection. Three of them had adenomas >5 cm that failed to regress despite of cessation of oral contraceptives. In one patient malignancy could not be excluded. Five patients (28%) suffered complications from surgical treatment.In conclusion, observation of adenomas <5 cm is justified due to improved radiological diagnosis and follow-up.

A Blinded, Randomized, Sham-Controlled Trial of Endoscopic Gastroplication for the Treatment of Gastro-Esophageal Reflux Disease (GERD)

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Endotherapy for GERD is rapidly emerging, but there is a great need for randomized controlled trials to evaluate efficacy. In a single-centre, double-blinded, randomised, sham-controlled trial 60 patients (36M/24F; mean age, 46 years) with daily GERD symptoms and abnormal esophageal 24-hr pH monitoring were randomly assigned to either three plications (n=20) using the Endocinch suturing system (BARD), a sham procedure (n=20) or observation (n=20). Excluded were patients with a hiatal hernia >3 cm or grade C/D esophagitis. The placebo effect was evaluated by comparing the observation group with sham. Primary endpoints were proton pump inhibitor use and GERD symptoms. Secondary endpoints were quality of life (SF-20), esophageal acid exposure, esophageal manometry and the occurrence of adverse events. Follow-up assessments were performed at 3 months.
All 40 procedures were performed in an outpatient setting under conscious sedation. Mean procedure time was 43 min in the Endocinch group (range 26-75) and 40 min in the sham group (preset time). One patient received only 2 plications due to technical failure. At 3 months, the percentage of patients that had reduced medication use by $\geq$50% was greater in the active treatment group (65%) than in the sham (25%) or the observation group (0%) ($p<0.02$). GERD symptoms improved more in the active group than in the sham group; heartburn frequency and severity (both $p<0.01$) and regurgitation frequency ($p=0.02$). Three SF-20 quality of life subscales (role function, general health, bodily pain perception) improved in the active group vs. sham. Esophageal acid exposure (% pH<4) decreased modestly after active treatment ($p=0.02$), but not significantly different from the sham group (-2.7% vs. -1.9%; $p=0.61$). There were no changes in esophageal manometry characteristics. The occurrence of transient dysphagia after active treatment was highly predictive for a better treatment outcome (OR 13.5; $p=0.035$). No serious adverse events occurred.
Conclusions: Endoscopic gastroplication, using the Endocinch device, reduced acid inhibitory medication use, improved GERD symptoms and improved the quality of life at 3 months compared with a sham procedure. However, the reduction in esophageal acid exposure was not greater after endoscopic treatment than after a sham procedure. Although this endoscopic antireflux procedure is attractive and safe, the results indicate that there is room for improvement.

One-year Follow-up after a Randomized, Sham-Controlled Trial of Endoscopic Gastroplication for the Treatment of Gastroesophageal Reflux Disease (GERD)

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Previously, we have shown in a randomized, sham-controlled trial that endoscopic gastroplication (Endocinch suturing system) reduced PPI use and GERD symptoms, and improved quality of life (QoL) after 3 months. Esophageal acid exposure was not significantly reduced compared with sham. The open-label, one-year results are now presented.

Sixty patients with daily symptoms of GERD and abnormal 24-hr esophageal pH-metry were randomly assigned to either three endoscopic gastroplications (n=20), a sham procedure (n=20) or observation (n=20). Excluded were patients with a hiatal hernia >3 cm or grade C/D esophagitis. At 3 months, after unblinding, 30 patients (sham, n=19 and observation, n=11) chose to cross over to active treatment. Patients without sufficient symptom relief were offered retreatment at least 3 months after first treatment. Thirty-two patients (23M/9F; mean age 45 years) completed the 12-month follow up and were analyzed. Pre-procedure and post-procedure assessments included PPI use (mean % from baseline dose), GERD symptoms and QoL at 3, 6, 9, and 12 months. Symptoms and QoL were scored 1 week off medications. Esophageal manometry and 24-hr esophageal pH monitoring were repeated at 3 months.

Ten of the 32 patients (31%) were retreated after a median follow-up of 4.0 (range 3-7) months with a mean of 1.3 extra plications. At 3, 6, 9 and 12 months, PPI use was reduced to 33%, 37%, 38% and 41% from baseline ($p<0.0001$ for all), respectively. 23 Patients (72%) improved upon intervention (defined as a ≥50% reduction in PPI use at 12 months). GERD symptoms scores (frequency x severity) improved up to 12 months follow-up, from 16.2 ± 5.5 to 7.9 ± 7.9 (mean ± SD for heartburn, $p<0.001$) and 15.2 ± 5.6 to 8.2 ± 8.1 (regurgitation, $P<0.001$). Three of six SF-20 QoL subscales improved up to 12 months: physical function ($p=0.02$), general health ($p<0.01$) and pain perception ($p<0.001$). Esophageal acid exposure (% pH<4) decreased from 9.1% to 7.2% at 3 months (n=20), but this was not statistically significant ($p=0.10$). Manometry outcomes did not change after treatment. One serious adverse event occurred: a mucosal tear requiring short clinical observation.

Conclusions: After one year, endoscopic gastroplication reduces PPI use, improves GERD symptoms and quality of life in a majority of patients, although the reduction in esophageal acid exposure is small and a considerable number of patients require retreatment.

Bone Morphogenetic Protein (BMP)-4-mediated transformation of inflamed squamous esophageal mucosa into Barrett's esophagus.

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Background: To identify genes specifically involved in the transformation of squamous epithelium into Barrett's esophagus (BE), we previously used SAGE to compare the expression profile of BE with normal squamous esophagus (SQ) and gastric cardia mucosa. BMP4 was found to be uniquely expressed in BE. The aim of this study was to investigate the potential role of BMP4 in the metaplastic development of BE.
Material and Method: Immunoblotting was performed on patient biopsies of BE, SQ and inflamed SQ mucosa for the presence of BMP4 and protein members of the BMP pathway i.e. BMP Receptor IA and II, Smad 4, P-Smad 1/5/8 and ID2. Furthermore, primary cell cultures of biopsy specimens of SQ and BE were established. The primary cell cultures of SQ cells were treated with rec. h. BMP4 and the BMP4 pathway was investigated by immunoblotting. Immunohistochemistry was performed for analysis of the Cytokeratin (CK) expression pattern and microarray analysis was done to analyze and compare the gene expression profiles.
Results: Immunoblotting revealed BMP4 expression and activation of associated signaling in BE and inflamed SQ mucosa but not in normal SQ. Upon treatment of SQ cells with BMP4 the level of P-Smad 1/5/8 was increased, this was blocked through addition of the BMP antagonist Noggin. Phenotipically, a shift of the CK expression pattern, of the BMP4 treated SQ cells towards that of columnar cell type was found with upregulation of CK7 and CK20 and downregulation of CK10/13. Finally analysis by microarrays demonstrated a shift of the gene expression profile of the BMP4 treated SQ cells towards that of BE cells.
Conclusion: BMP4 is a keyplayer in the transformation of inflamed esophageal mucosa into BE. We propose that the premalignant metaplasic development of BE is mediated by BMP4 and that inhibition of BMP4 signaling offers a novel avenue for the therapeutic management of this disease.

Genotype-phenotype correlations as a guide in the management of familial adenomatous polyposis

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The options for prevention of colorectal cancer in familial adenomatous polyposis (FAP) is either a colectomy with ileorectal anastomosis (IRA) or a total proctocolectomy with ileal-pouch-anal anastomosis (IPAA). Rectal cancer risk is eliminated by IPAA, but complication rate is higher than in IRA. Mutation analysis could predict severity of polyposis in FAP patients and may be helpful in the surgical decision making.Patients with an IRA were selected from the Dutch Polyposis Registry. Patients were subdivided according to the site of mutation into three groups: the attenuated (group 1), intermediate (group 2) and severe (group 3) genotype. The cumulative risks of secondary rectal excision and rectal cancer were calculated for each group. We also evaluated the outcome of surgery in patients with a MUTYH mutation.Between 1956 and 2004, 177 patients with a known APC mutation underwent an IRA including 28 patients from group 1, 121 from group 2 and 28 from group 3. The cumulative risk of rectal cancer 15 years after surgery was 0% in group 1, 3% in group 2 and 8% in group 3. The cumulative risk of rectal excision 20 years after surgery was 4% for group 1, 32% for group 2 and 65% for group 3. The risk of rectal excision was significantly higher in group 3 than in the other groups ($p<0.05$). Thirteen patients with a MUTYH mutation underwent IRA; none of them needed secondary rectal excision and no rectal cancer was reported.
Conclusion: The risk of secondary rectal excision and rectal cancer after IRA can be predicted on the basis of the APC mutation site. An IRA appears to be the treatment of first choice in patients with a mutation associated with the attenuated phenotype. Patients with a mutation associated with severe polyposis are good candidates for an IPAA.

Sustained virological response leads to an improved clinical outcome in patients with hepatitis C and advanced fibrosis

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Patients with chronic hepatitis C patients may develop decompensated liver disease and hepatocellular carcinoma (HCC). This risk is highest in patients with advanced fibrosis. Treatment with interferon or pegylated interferon may lead to sustained virological response (SVR), which means undetectable virus at six months after treatment. However, it remains uncertain whether sustained responders have a better clinical outcome than non-responders. The aim of this study is to investigate whether SVR leads to an improved clinical outcome in Western patients with hepatitis C and advanced fibrosis.In this retrospective international multicenter cohort study we included 541 patients with advanced fibrosis/cirrhosis (Ishak 4-6), with a mean follow-up of 3.3 years. Three hundred fifty-eight patients had received interferon ± ribavirin and 276 had received a regimen containing pegylated interferon ± ribavirin. Seventy-one percent were non-responders (NR) and 29% achieved an SVR.In multiple regression analysis, genotype 1 and previous non-response were associated with a smaller probability of achieving an SVR, whereas higher pre-treatment albumin levels and treatment with pegylated interferon were associated with a higher probability of achieving an SVR.The five-year occurrence of hepatic failure and HCC was 0% and 5.6% (95% CI 0.0-12.1) among sustained responders versus 12.2% (95% CI 8.1-16.3) and 8.2% (95% CI 4.4-11.9) among NR ($p<0.01$ for liver failure and $p=0.04$ for HCC). The five-year occurrence of liver-related death was 2.4% (95% CI 0.0-7.1) among sustained responders and 10.1% (95% CI 6.0-14.3) among NR (Log Rank $p<0.01$). Time dependent Cox regression analysis showed that SVR, older age, higher pre-treatment bilirubin, lower albumin levels and lower platelet counts are independently associated with the development of clinical events during follow-up. In conclusion, SVR to (peg)interferon leads to an improved clinical outcome in patients with hepatitis C and advanced fibrosis.

Endoscopic Tri-Modal Imaging (ETMI) for the Detection of Dysplastic Lesions in Barrett's Esophagus

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The ETMI system (Olympus, Tokyo, Japan) incorporates high-resolution endoscopy (HRE), autofluorescence imaging (AFI) and narrow band imaging (NBI) in a single device. The system uses an endoscope with 2 CCD chips; one for HRE and NBI (with an optical zoom function) and one for AFI. In the AFI mode, real-time images are constructed using a new algorithm based on total tissue autofluorescence and green reflectance. The aim of this multi-center feasibility study was to investigate the diagnostic potential of ETMI and the relative contribution of each modality for the detection of dysplasia in Barrett's esophagus (BE). The esophagus of BE pts was first inspected with HRE followed by AFI for the detection of additional suspicious lesions. All lesions detected with HRE or AFI were subsequently inspected by NBI using the zoom mode to evaluate the presence of abnormal mucosal and microvascular patterns followed by biopsies for blinded histopathological assessment. Standard surveillance biopsies were also performed. 23 pts have been assessed with the ETMI system to date, including 9 pts referred for inconspicuous dysplasia and 14 pts participating in a standard surveillance program.Per patient assessment: 6 pts were diagnosed as having high-grade dysplasia (HGD), and 4 of them had lesions detected with HRE and AFI. In one of these pts, AFI detected an additional lesion with HGD that was missed under HRE. In 2 pts, no abnormalities were seen with HRE and HGD was solely diagnosed with AFI. In total, 9 pts were diagnosed with low-grade dysplasia (LGD) or HGD. In 5 pts, dysplastic lesions were detected with HRE and AFI. In 4 pts, LGD or HGD was detected only with AFI.Per lesion assessment: 30 suspicious lesions were identified with AFI; 7 of these contained HGD, the remaining 23 (77%) were found to be false-positives for HGD. With detailed characterization of these lesions using NBI, 5 of the 7 lesions containing HGD were classified as suspicious. 7 of the 23 false-positive lesions were also classified as suspicious thereby reducing the overall false positive rate to 23%. AFI appears to enhance the detection of dysplastic lesions relative to HRE. However, AFI seems to be associated with a high false-positive rate which may be reduced with the addition of NBI. The potential of ETMI for enhancing lesion detection in BE is promising but a more accurate assessment of its diagnostic performance will be obtained as more patients are enrolled in this ongoing study

Stepwise endoscopic resection of the whole Barrett's esophagus in patients with early neoplasia effectively removes all genetic alterations from the esophageal epithelium.

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Malignant transformation of Barrett's esophagus (BE) is associated with several genetic events that accumulate as the mucosa becomes dysplastic and develops into adenocarcinoma. Stepwise radical endoscopic resection (SRER) of BE with high grade intra-epithelial neoplasia (HGIN) or early cancer (EC) is a promising new treatment for BE, which results in complete re-epithelialization of the resected area with neo-squamous epithelium. However, it is not known whether SRER eradicates pre-existing genetic abnormalities. The aim of this study was to prospectively evaluate whether genetic abnormalities as found before SRER are effectively eradicated and absent in the neo-squamous epithelium.Nine consecutive BE patients with HGIN or EC who underwent SRER were included in this study. Immunohistochemistry (IHC) for assessing proliferation (Ki-67) and p53 over-expression, and DNA Fluorescent In Situ Hybridization (FISH) were performed on endoscopic resection (ER) specimens of the BE and on biopsies of the neo-squamous epithelium taken during follow up. DNA-FISH was performed to determine aneusomy with centromeric probes for chromosomes 1 and 9, and with locus specific probes for assessing loss of the tumor suppressor genes p16 and p53. FISH results were blindly scored by two experts. A minimum of 100 nuclei were scored for each DNA-FISH probe. Lymphocytes in the ER-specimens were used as controls. Nine pts were included (3 HGIN, 6 EC). FISH results showed that all pts had genetic alterations in their ER specimens. All pts showed hyperploidy for chromosome 1 and 5 pts for chromosome 9. Four had loss of chromosome 9. Loss of p16 was seen in 7 patients, while 8 patients proved to have loss of p53. IHC results showed that 7 pts had intense p53 nuclear staining in 100% of cells, indicating p53 mutations, while 2 pts were negative for p53. All pts had Ki-67 positive surface epithelium, indicating an increased proliferation index. In contrary to these pre-treatment findings, all post-treatment biopsy specimens showed a normal diploid signal count for all DNA-FISH probes. Furthermore, in all neo-squamous cases normal IHC staining for Ki-67 and negative staining for P53 was seen.Conclusions: Stepwise radical endoscopic resection of the complete Barrett's esophagus with early neoplasia successfully eradicates pre-existing genetic abnormalities such as aneusomy and loss of p16 and p53 and results in neo-squamous epithelium without these genetic abnormalities.

Circumferential balloon-based radiofrequency ablation of Barrett's esophagus in patients with low-grade or high-grade dysplasia with and without a prior endoscopic resection using HALO360 Ablation System

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Aim: Circumferential balloon-based radiofrequency (RF) energy ablation of Barrett's esophagus (BE) has proved safe and effective for non-dysplastic BE. This study assesses the efficacy and safety of RF ablation in patients with BE containing LGD or HGD +/- prior endoscopic resection (ER).
Methods: Eligibility: BE 2-7 cm with LGD or HGD from ≥ 2 EGD sessions, visible abnormalities removed by ER prior to ablation and esomeprazole 40 mg BID during study. The HALO360 Ablation System (BÂRRX Medical, Sunnyvale, CA) consists of a balloon-based electrode array delivering high power (300 W) RF energy to the BE tissue in < 1sec. Energy density (12 J/cm2) and balloon pressure are controlled, enabling uniform ablation depth. At baseline and 10 weeks, ablation was performed from the proximal margin of BE to the gastric folds. Post-ablation symptoms (odynophagia, dysphagia, chest, throat and abdominal pain) were assessed by 14-day visual analog scale (0-100 mm, VAS) survey. At 4 months, EGD, Lugol's staining and biopsies (4Q/1cm) were performed and histology was reviewed by an expert pathologist. Primary endpoint was complete response (CR) defined as absence of dysplasia at 4 months. Secondary endpoints: safety, VAS scores and surface area regression of BE. Results: 11 pts (8 men, median age 60 yrs, IQR 55-67) were treated (median BE length 5cm, IQR 3-7). 6 pts had prior ER with early carcinoma (n=2), HGD (n=1) and LGD (n=3) in the resection specimens. Baseline diagnosis after ER and prior to ablation was LGD (n=1) and HGD (n=10). After 2 sessions, 10/11 patients are in CR for dysplasia (91% CR rate). The patient with persistent dysplasia, went from HGD to LGD and has only small residual islands of BE left. Procedures were performed on an outpatients' basis. There were no serious adverse events, i.e., no strictures or buried glands. The median day 1 VAS was 27/100 (IQR 0-53) for chest pain, returning to 0/100 by day 5. The median day 1 VAS for other symptoms was 0/100 (max IQR 0-23 for odynophagia). Median BE regression was 90% (IQR 80-95) at 10 weeks, and 99% (IQR 95-99) at 4 months. Conclusions: Circumferential RF ablation using the HALO360 Ablation System appears to be a safe and effective treatment for BE with LGD or HGD, with a 91% CR rate for dysplasia and minimal side effects. Patients now have very limited residual BE (mostly non-dysplastic) and are candidates for completion of treatment with a focal ablation device utilizing the same electrode array technology

Histological evaluation of resection specimens obtained at 244 endoscopic resections in Barrett's esophagus

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Aim was to study the histological evaluation of endoscopic resection (ER) specimens of early neoplastic lesions in Barrett's esophagus (BE).Routine histological evaluations of specimens obtained at all ERs in BE performed between '00-'05 were evaluated. Specimens were pinned down on paraffin (mucosal side up) and immediately fixed in 4% formalin. No attempts were made to reconstruct the specimens after piece-meal resection. Specimens were cut in 2 mm slices. Standard H&E staining was performed on 4 µm slides and, if necessary, supplemented with p53 and Ki-67 immunohistochemical staining. Evaluations were performed by two experienced pathologists.244 ERs were performed for low-grade intraepithelial neoplasia (LGIN) in a mass (n=1), high-grade intraepithelial neoplasia (HGIN) (n=82), early carcinoma (EC) (n=53) or removal non-dysplastic BE (n=108) for stepwise radical endoscopic resection (SRER). In 194 ERs a piece-meal resection was performed: 97 for HGIN/EC and 97 for SRER with median 3 resections (IQR 2-5). A total of 921 specimens were obtained.Histology revealed no dysplasia in 48 ERs (all SRER), LGIN in 42, HGIN in 89, T1m in 50, and T1sm in 15 ERs. Fifty cancers (77%) were classified well differentiated (G1). Moderately (G2) or poorly (G3) differentiated lesions were found in 8 (12%) and 7 (11%) cancers, respectively. G2-3 cancers significantly more often invaded the submucosa than G1 cancers (10/15 vs. 5/50, $p<0.001$). One G3 T1m3 (penetration into second muscularis mucosae layer) tumor showed lymph vessel invasion. In none of the specimens vascular invasion was observed.Specimens of 14 ERs (5%) had a deeper margin positive for neoplasia. Significantly more G2-3 cancers were irradically removed (6/15 vs 6/50; $p=0.024$). Of the en-bloc resections, only 8 out of 52 specimens (22%) had lateral margins free of HGIN/EC. Mechanical and thermal artefacts interfering with the histological evaluation were seen in 61 (23%) procedures.Most endoscopically resected early neoplastic lesions in BE contain HGIN or G1 mucosal cancer and have a deeper margin free of neoplasia. Submucosal invasion is associated with a poorer differentiation grade and invasion into lymph or blood vessels are rare findings. The majority of ERs require piece-meal resection and if an en-bloc resection is attempted, only the minority has lateral resection margins free of dysplasia. In addition, artefacts affect histological evaluation in a significant percentage of specimens.

Endoscopic resection in esophagus and stomach is safe: a prospective analysis of 303 procedures

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Aim was to prospectively evaluate the safety of endoscopic resection (ER) for early neoplasia in esophagus and stomach. All ERs performed from '00-'05 in esophagus or stomach were included. Complications were divided into “acute” (during the ER), “early” (< 48 hours after ER) or “delayed” (>48 hours). 303 ER procedures were performed; 274 in the esophagus (261 Barrett’s esophagus (BE), 13 squamous esophagus) and 29 in the stomach. Indications were low grade intraepithelial neoplasia (LGIN) in a lesion or mass (n=5), high grade intraepithelial neoplasia (HGIN) (n=100), early carcinoma (EC) (n=73) and removal of non-dysplastic BE for stepwise radical endoscopic resection (SRER; n=125). 231 ERs were performed with the cap technique (74 large flexible cap (18 mm), 157 hard cap (12 mm)), 66 with multi-band mucosectomy (MBM), and 6 with the lift-and–snare technique. In 229 ERs a piece-meal resection was performed with median 3 (IQR 2-5) resections. Specimens removed with the large cap had a mean diameter of 23 mm (SD 5.8), with the standard cap 20 mm (SD 5.0) and with the MBM cap 17 mm (SD 6.0). Histology revealed EC in 83, HGIN in 104, LGIN in 33, and no dysplasia in 83 specimens (all SRER).“Acute” complications occurred in 53 ERs (17%): 50 bleedings, 3 perforations. These bleedings were all effectively treated with haemostatic techniques and classified “mild”; none of the pts had a drop in hemoglobin levels or required blood transfusions. The perforations were all classified as “severe”; 2 esophageal perforations were treated conservatively and 1 gastric perforation was closed surgically. Six (2%) “early” complications occurred, all bleedings effectively treated with repeat endoscopy, and classified moderately severe. 18 complications (15 acute bleedings, 1 perforation, 2 early bleedings) occurred in 74 ERs with the large cap (24%), 33 (29 acute bleedings, 2 perforations, 2 early bleedings) in 157 ERs with the standard cap (21%), and 7 (6 acute bleedings, 1 early bleeding) in 66 (11%) MBM ERs (MBM vs. standard p=0.03, others NS). “Delayed” complications developed in 30 pts who had a symptomatic stenosis treated with dilatations and/or temporary stent placement.ER in esophagus and stomach is safe. Most complications become apparent immediately during the ER and can be managed endoscopically. Bleeding after the ER and severe complications (i.e. perforations) are rare (2% and 1%). Complications appear to occur less frequent with the MBM-cap technique.

The burden of upper gastrointestinal endoscopy in patients with Barrett's esophagus

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Upper gastrointestinal (GI) endoscopy is an invasive diagnostic procedure that causes pain, discomfort and psychological distress in patients. Regular endoscopic surveillance, as recommended for patients with Barrett's esophagus (BE), may therefore be experienced as burdensome by patients. To what extent it is experienced as burdensome and whether the burden decreases when patients get used to it is unknown. We prospectively assessed the burden of upper GI endoscopy in BE patients under regular surveillance and in a control group of patients with non-specific upper GI symptoms, and investigated whether these groups perceived the burden of endoscopy differently.A total of 394 patients (180 BE patients and 214 patients with non-specific GI symptoms) filled out questionnaires one week before, on the day of, one week after and one month after upper GI endoscopy. Inclusion criteria were a BE segment of at least 2 cm for the BE group, and dyspepsia without alarm symptoms for the control group. Four variables were assessed: 1) pain and burden experienced during endoscopy, 2) symptoms, 3) psychological distress levels (Hospital Anxiety and Depression scale and Impact of Event Scale), and 4) perceived risk of developing a malignancy.Patients with non-specific GI symptoms were diagnosed with a hiatal hernia (45%), non-specific gastritis (25%), reflux esophagitis (20%), and other (10%). Of all patients, only 16% experienced pain from the endoscopy. However, 87% reported it to be burdensome. Apart from an increase in sore throat (47% after endoscopy versus 22% before) the procedure did not cause symptoms. Patients' distress levels were increased in the week prior to the endoscopy compared to the week after. BE patients experienced significantly more burden from the endoscopy (i.e. 7% reported no burden versus 20% of the control group) but reported lower distress levels compared to the control group. Patients with a higher risk perception did not report a higher burden or more psychological distress. Having had more previous endoscopies was associated with lower distress levels as measured by the Impact of Event Scale.
Conclusion: Upper GI endoscopy is burdensome for patients and causes moderate psychological distress. Repeat endoscopies may reduce distress but increases the burden experienced from the procedure in BE patients. Recommendations for endoscopic surveillance should take into account the burden and distress of upper GI endoscopy for patients.

Large diameter stents are associated with a lower risk of recurrent dysphagia than small diameter stents

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Stents are used for the palliation of dysphagia from obstructing esophagogastric cancer. A drawback of stents is the occurrence of recurrent dysphagia. Large diameter stents have been introduced for the prevention of stent migration. However, it has been suggested that the extra pressure on the esophageal wall exerted by large diameter stents may cause more complications. The aim of the study was to compare large and small diameter stents for the risk of developing complications and recurrent dysphagia in patients with malignant dysphagia.Between 1996 and 2004, 375 patients with dysphagia due to obstructing esophageal and gastric cardia cancer were treated with either small (22-24 mm; n=311) or large (28-30 mm; n=64) diameter stents. All patients were prospectively followed by telephone interviews or home visits by a research nurse. The risk of developing stent-related complications or recurrent dysphagia was calculated with logistic regression analysis with the covariates age, gender, tumor length, tumor location, prior radiation and/or chemotherapy, and type and diameter of stent. Factors significantly related to the outcome in univariate analysis were included in a multivariate model.Complications (pain [49], bleeding [45], reflux [27], perforation [14], fever [11] and fistula [7]) occurred in 141 (38%) patients. Major complications to the esophageal wall (bleeding, perforation, fever, fistula) were not different between patients with small or large diameter stents (56 [18%] vs. 13 [20%]; adjusted odds ratio (OR): 1.22; 95%CI 0.62-2.41). Pain following stent placement was also not different between patients with small or large diameter stents (36 [12%] vs. 13 [20%]; adjusted OR: 1.65; 95%CI 0.73-3.72). Recurrent dysphagia occurred in 107 (29%) patients and was caused by migration (n=52), tumor/tissue regrowth (n=43) and food bolus impaction (n=29). Recurrent dysphagia was more common in patients with small diameter stents than in patients with a large diameter stents (99 [32%] vs.8 [13%]; adjusted OR: 0.28; 95%CI 0.12-0.64). Particularly stent migration occurred less frequently with a large diameter stent (50 [16%] vs. 2 [3%]; adjusted OR: 0.17; 95%CI 0.04-0.77).Conclusion: Large diameter stents are probably safe for the palliation of malignant dysphagia. In addition, large diameter stents are associated with a lower risk of developing recurrent dysphagia compared to small diameter stents.

Effect of endoscopic gastroplication on acid and weakly acidic gastroesophageal reflux: a study using impedance monitoring

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In the evaluation of several endoscopic antireflux procedures a discrepancy in the degree of improvement between symptoms and objective reflux parameters has been reported. We aimed to perform an in-depth analysis of the effect of endoscopic gastroplication on esophageal reflux using combined pH-impedance recording. 10 patients with GERD (9 men, mean age 48 years, range 36-58) and no hiatal hernia were included. They were treated with 3 endoscopic gastroplications (Endocinch™ suturing system) and underwent 24hr pH-impedance monitoring before (pre) and 3 months after treatment (post). Acid inhibitory drugs were discontinued 1 week before recordings. Analysis of the pH-impedance signals included total reflux time, number of reflux episodes according to reflux content (acid, weakly acidic and weakly alkaline), gas-liquid composition (gas only and liquid containing) and proximal extent of the refluxate. Total and upright reflux times assessed by impedance were significantly decreased after treatment (total reflux time pre and post: 2.2 and 1.5%, p=0.008; upright reflux time pre and post: 4.2 and 2.4%, p=0.007), but not when assessed by pH-metry. The total number of reflux episodes was significantly reduced after treatment as measured by both impedance (pre: 99, post: 70, p=0.006) and pH monitoring (pre: 63, post: 40, p=0.04). There were comparable non significant reductions in acid and weakly acidic reflux episodes as measured by impedance. A significant reduction in the number of liquid containing reflux episodes was found (p=0.01), whereas the gas only reflux episodes were not significantly decreased. Mean acid and volume clearance times as well as proximal extent of the refluxate were unaffected by the procedure as assessed by pH-metry and impedance monitoring. Conclusions: Endoscopic gastroplication leads to a reduction in gastro-esophageal reflux of all types (acid/weakly acidic, liquid/gaseous, upright/supine). The proximal extent of reflux is not affected by the procedure.

Endoscopic pancreatic duct decompression in treating pancreatic leakage: a successful and safe method in selected patients

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Pancreatic leakage can occur as a consequence of abdominal trauma, acute pancreatitis or pancreatic surgery and is associated with considerable morbidity and even mortality. The best strategy in these patients is not known, external drainage is most often performed and results in pancreatic fistulas with increased morbidity. Small series suggest that in selected cases decompression of the pancreatic ductal system through transpapillary stentplacement or sphincterotomy can achieve resolution of leakage. We therefore studied the efficacy of endoscopic treatment in patients with persistent pancreatic leakage after surgery, trauma or pancreatitis.Patients were identified from a database containing all endoscopic procedures in our institution between 2003 and 2005. Indications for ERCP were persistent symptomatic peripancreatic effusions with increased amylase activity. Follow-up ranged from 3 months to 2 years. The charts of all patients were reviewed.ERCP was attempted in 25 patients (14 male; median age 51 yrs, range 8-73). Pancreatic injury was related to surgery (n=10), trauma (n=5) or pancreatitis (n=10). Pancreatic duct decompression with either stentplacement (n=19), or PD sphincterotomy (n=3) was technical successful in 22 patients (88%). Reasons for technical failure were BII anatomy, duodenal oedema and unsuccessful selective canulation. Successful long term outcome, defined as recovery without additional surgical or radiological procedures, was achieved in 76% (n=19) and failed in 24% (n=6). Three of six patients were in the pancreatitis group and three in the postoperative group (p=0.16 vs. trauma). In 10 patients repeat procedures were necessary due to stent dysfunction. Long term outcome was different in patients with leakage in either head or body area (6/11 successful; 55%) versus patients with leakage in the tail area (13/13 successful; p=0.006). Three (12%) patients died ; one in the postoperative group and two in the pancreatitis group. Stentplacement was successful in these patients and their deaths were unrelated to the procedure. In linear regression analysis only location of the leak was predictive of outcome (p=0.034), and not age, sex, indication, PD sphincterotomy or bridging of the leak with stentplacement. Conclusions: endoscopic pancreatic ductal decompression is a highly effective method to treat pancreatic leakage in postoperative, trauma and pancreatitis patients, especially when the leak is located in the tail area.

Endoscopic ultrasound (EUS) guided transgastric drainage followed by endoscopic necrosectomy in patients with infected pancreatic necrosis: a retrospective cohort study

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Infection of necrosis after acute necrotizing pancreatitis is potentially life threatening, with mortality rates around 35%. Surgical necrosectomy by laparotomy has been the treatment of choice for many years. However, there is a tendency towards minimally invasive procedures to reduce morbidity and mortality. Data on safety and feasibility of minimally invasive approaches are scarce. We therefore wished to evaluate the feasibility, safety and outcome of EUS-guided drainage followed by endoscopic necrosectomy of infected pancreatic necrosis in 8 consecutive patients (5 females, 3 males, age 38-65, median 50) in a retrospective cohort study (period: Jan 02 – Dec 05). In all patients, EUS was used to visualize the extent of the necrosis and to determine the optimal puncture site. Under EUS, a transgastric puncture was performed using a 19 Gauge needle through which a 0.035 inch guide wire was advanced in the necroma under fluoroscopic guidance. Using the outside sheath of a cystogastrotome a hole was burned in the stomach wall, followed by balloon dilation of the tract up to 8mm. Thereafter, 2 double-pigtail stents and a nasocystic catheter were placed in the necroma in all patients. During the subsequent days, the site of access was dilated up to 15mm and a forward viewing endoscope was advanced into the retroperitoneum. The necrotic debris was evacuated with a basket and the cavity was rinsed with saline. This procedure was repeated until all necrotic material was removed and the granulation tissue lining the cavity was everywhere visible. All patients received broad spectrum antibiotics.Initial EUS guided drainage was successful in all patients. Two (range 1-6) subsequent endoscopic necrosectomies were necessary to remove all necrotic material. In one patient the first necrosectomy was complicated by leakage of free air in the abdominal cavity, necessitating urgent surgical intervention. He died 4 months later due to multi organ failure. One other patient needed surgical drainage, because endoscopic necrosectomy could not sufficiently remove all the necrotic tissue. Six patients (75%) fully recovered without relapse during follow-up (1-20 months, median 6). One other procedure was complicated by minor bleeding.
Conclusion: EUS guided drainage and subsequent endoscopic necrosectomy in patients with infected pancreatic necrosis appears to be feasible, and may avoid surgery in most patients. However, life threatening complications can occur.

Trends and forecasts for hospital admissions for acute and chronic pancreatitis in the Netherlands.

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Background: The incidence and prevalence of acute and respectively chronic pancreatitis seems to be increasing in the Western countries in recent decades. As part of an ongoing Dutch prospective cohort study, we investigated the trends in hospital admissions for acute and chronic pancreatitis from 1992 to 2004 and calculated the predicted admissions up to 2010. Methods: We retrospectively analyzed the hospital discharge data accumulated by Prismant Health Care Information. This organization maintains a nationwide, automated database that collects anonymous data on all hospitalizations in the Netherlands. All primary hospital admissions for acute and chronic pancreatitis (ICD-9, 577.0 and 577.1) from 1992 to 2004 were identified. For analysis of the future trends in hospital admissions we used linear and curvilinear regression models. During prediction the model with the highest R2 was chosen, unless more conservative estimates were attained with a simple linear model not below 5% of the highest R2.Results: In 1992 there were 1785 hospital admissions for acute pancreatitis registered. In 2004 this number raised to 3120, representing an increase of 75% over a 12 year time period. The linear regression model (R2=97.1%) predicted 3344 (95% CI, 3130-3557) and 3680 (95% CI, 3444-3916) admissions for 2007 and 2010, respectively. This reflects a steady and further increase of hospital admissions for acute pancreatitis by an additional 18% in 2010 compared to 2004. In the same 12 year time period the hospital admissions (> 1day) for chronic pancreatitis showed an increase of 75% (from 790 to 1386 admissions). The cubic regression model fitted best (R2=91.3%) for the description of the trend in admissions from 1992-2004. Using this model, the predicted admission rate for respectively 2007 and 2010 are 2246 (95% CI, 1708-2785) and 3830 (95% CI, 2446-5234) admissions. The number of single day hospital admissions from 1992-2004 almost tripled from 37 to105 admissions (184% increase), reflecting technical advancements in endoscopic diagnostic and therapeutic procedures for CP in daycare setting such as ERCP and EUS.Conclusions: Hospital admissions for both acute and chronic pancreatitis have increased substantially from 1992-2004. This trend will most likely continue for the near future. Consequently, it can be anticipated that the burden and costs of pancreatitis admissions to the Dutch health care system will further increase.

High-resolution endoscopy and the additional value of chromoendoscopy in the evaluation of duodenal polyposis in FAP-patients.

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Introduction: Duodenal polyps occur in approximately 90% of all patients with familiar adenomatous polyposis (FAP). An estimated 5% of them develop duodenal cancer, nowadays being the leading cause of death in FAP-patients. Endoscopic surveillance of the duodenum has become standard care in these patients. Guidelines for endoscopic surveillance have been developed in which the interval is dependent on the Spigelman-classification (including number, size and histology of the polyps). Since the introduction of these guidelines, the quality of endoscopic imaging has dramatically improved and chromo-endoscopy has further enhanced our ability to detect small polyps.
Aim: To investigate the use of high-resolution endoscopy and the additional value of chromoendoscopy in the evaluation of duodenal polyposis in FAP-patients.
Methods: All consecutive FAP-patients scheduled for a surveillance endoscopy in 2 academic centers underwent gastroduodenoscopy with high-quality forward- and sideward-viewing endoscopes. After scoring the number and size of polyps in the duodenum, indigocarmine 0.5% was sprayed onto the mucosa and the polyps were scored again. Biopsies were taken from the larger lesions and the papilla and were evaluated by an expert pathologist.
Results: A total of 47 endoscopies were performed in 39 patients (19 men, mean age 48 yrs) were examined. Before the application of dye, in 37 patients (95%) duodenal polyps were seen. Spigelman-classifications were: stage 0, 2 patients (5%); stage I, 2 patients (5%); stage II, 9 patients (23%), stage III, 13 patients (33%) and stage IV, 13 patients (33%). The papilla was enlarged in 21 patients (54%); biopsies revealed dyplasia in 18 (46%). Chromoendoscopy detected more duodenal polyps in 13 procedures (mean # of polyps 27 vs 30, p=0.03) and maximum size of the polyps increased in 5 (15 vs 16 mm, NS). The total number of points for the Spigelman-classification was increased in 7 procedures. However, this resulted in an increased Spigelman-classification in only 3 (6.4%).
Discussion: Compared to historic endoscopic studies evaluating duodenal polyposis in FAP-patients, the use of high-resolution endoscopes results in increased polyp detection and subsequently a higher Spigelman-score. Although chromoendoscopy detected significantly more polyps, this resulted in a higher Spigelman stage in only 6% of endoscopies and therefore its additional value seems to be limited compared to high-resolution endoscopy.

Double Balloon Enteroscopy :Clinical outcome in 142 Overt- and occult gastro-intestinal bleeding (OGIB) patients

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Until the introduction of the Double Balloon Enteroscopy, only the proximal small bowel and terminal ileum were accessible for diagnostic and therapeutic endoscopy. We describe our experience in a group of patients with overt and occult gastro-intestinal bleeding (OGIB) with no focus with other conventional endoscopic methods. Patients were examined and treated with the double balloon enteroscopy (DBE) (Fujinon®) for enteroscopy.
Between November 2003 and December 2005, 142 OGIB patients with negative findings during upper- and lower endoscopy were referred to our hospital. Patient characteristics, DBE findings, treatment and complications are described. For DBE all endoscopic interventional options were available. All patients were monitored for complications (48 hours).
Hundred seventy two DBE procedures were performed in 142 patients (MF ratio1,09) with a mean age of 65 ±SD 15 years. Some patients needed ≥2 DBE procedures. Anterograde DBE was chosen in 140, 12 of them had retrograde DBE later on, 10 patients had only retrograde approach and 20 patients had both approaches on the same day. Responsible lesions were recognized in 105/142 (73.9%) patients and 62 patients could be treated. Active bleeding in 17 patients, angiodysplasias in 50 patients, ulcers in 11 patients, 6 patients with lesions suspicious for tumours: metastasis melanoma (n=1), B-cel lymphoma and (n=2) and carcinoid (n=1), in 4 patients small bowel diverticulosis was found and in 2 cases multiple polyps. In 7 patients DBE technically failed (negative introduction of terminal ileum, thoracal hernia diafragmatica and non progression in duodenum/jejunum).
Patient tolerability otherwise was good and complication rate was acceptable. One patient had moderate acute pancreatitis and one patient was admitted for 24 hours observation due to abdominal pain.
Conclusion: This large pilot cohort shows that DBE is a well tolerated, safe and effective endoscopic technique with a high diagnostic yield and therapeutic opportunities.

The tumor suppressor gene p53 as a predictor for development of esophageal cancer in patients with achalasia

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Introduction: Patients with longstanding achalasia, an esophageal motor disorder leading to functional esophageal obstruction, have an up to 140x-increased risk to develop esophageal cancer. Chronic food stasis may lead to chronic inflammation, epithelial hyperplasia, multifocal dysplasia and squamous cell carcinoma (SCC). Gastro-esophageal reflux, a complication of LES-lowering therapy may lead to Barrett's metaplasia and adenocarcinoma (AC). Surveillance-endoscopies are advocated, however optimal sampling, analysis methods and surveillance intervals remain to be determined. Aim: To investigate whether p53(tumor suppressor gene) and Ki-67 (proliferation) expression, and changes in DNA-ploidy are early predictors for progression to malignancy. Methods: In our cohort of 414 achalasia patients, 4% died of advanced esophageal cancer despite bi-annual endoscopic surveillance. Out of those 16 cases, we selected 8 patients (5 males, mean age 45.5 yrs (30-66) at start of achalasia symptoms) who developed esophageal cancer (6 SCC, 2 AC). Cancer cases had been under surveillance for a mean of 8(2-20) yrs. All biopsy sets obtained during surveillance were studied for p53 and Ki-67 expression using immunohistochemistry. Two independent researchers counted the samples. Samples were considered positive for either marker if more than 15% of nuclei stained positive. Five patients (3 males, mean age 50(31-68) yrs at start disease) with achalasia without esophageal cancer development during follow-up (mean 19(18-20) yrs) served as controls. Results: 28 biopsy sets were obtained during surveillance in the cancer cases and compared with 25 sets from the controls. In 5/8 (62%) cancer patients (4 SCC, 1AC), p53 was expressed in previous surveillance biopsies at a mean time of 6(1-11) yrs prior to cancer development. In 1 SCC patient, p53 was negative, in 1 SCC patient the expression was 10% and in 1 AC patient not enough material was available. In the controls, no p53-expression was detected. Ki-67 was expressed in all surveillance biopsy sets of all carcinoma and control patients. Flow cytometry of surveillance specimens did not reveal aneuploidy. Conclusions: p53 expression, but not proliferation and changes in DNA-ploidy, appear useful to identify achalasia patients at increased risk of developing esophageal carcinoma. A prospective follow-up study is needed to determine the effectiveness of intense surveillance of p53-positive patients for early cancer detection.

Clinical impact of gene polymorphisms of matrix metalloproteinases and their inhibitors in gastric cancer

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Enhanced antigen levels of matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) are associated with clinico-pathological parameters of the tumors and survival of the patients. Single Nucleotide Polymorphisms (SNPs) in MMP- and TIMP-genes may be associated with disease susceptibility and might influence their antigen expression. We studied the genotype distribution and allele frequencies of SNPs of MMP-2, -7, -8 and -9 and TIMP-1 and -2 in gastric cancer patients in relation to tumor progression, patient survival, and tissue antigen expression.Genomic DNA was isolated from tissue of 79 Caucasian gastric cancer patients and from blood of 169 controls. Genotypes were analyzed by PCR based techniques. Antigen levels for MMPs and TIMPs were determined in tissue homogenates with specific ELISAs.Genotype distribution and allele frequencies of MMP-2, -7, -8, -9, and TIMP-1 and -2 were similar in gastric cancer patients and controls except for MMP-7-181 A>G. In addition, the genotype distribution of MMP-7-181 A>G was associated with H. pylori status (X2 7.8, P=0.005) and tumor-related survival of the patients. SNP TIMP-2303C>T correlated significantly with the WHO classification (X2 5.9, P=0.03) and also strongly with tumor-related survival (Log Rank 11.74, P=0.0006). SNPs of MMP-2, -8, -9 and TIMP-1 were not associated with tumor-related survival. Only the gene promoter MMP-2-1306 C>T polymorphism correlated significantly with the protein level within the tumors. First order dendrogram cluster analysis combined with Cox analysis identified the MMP-7-181 A>G and TIMP-2303C>T polymorphism combination to have a major impact on patients survival outcome.Conclusions: Determination of MMP-related SNPs, especially MMP-7-181 A>G and TIMP-2303C>T, might be useful to stratify and select patients for primary resection and (neo)-adjuvant treatment of gastric cancer aiming at better outcome.

Quality of life and the presence of symptoms in treated achalasia patients, a cross-sectional study

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To date health-related quality of life (HRQoL) as well the severity of symptoms has not been investigated using validated questionaires in treated achalasia patients who are not medical care seeking at the moment of their interview. The objective is to investigate the prevalence of symptoms and their impact on HRQoL in treated achalasia patients. A cross-sectional survey was conducted among 135 treated patients with achalasia, diagnosed with esophageal manometry, who visited our clinic between 2000 and 2005. Patients were approached by mail. The Short Form 36 Health Survey (SF-36) was used to measure HRQoL in patients and 113 sex- and age- matched healthy controls (HC). The frequency of dysphagia, regurgitation (none, occasionally, daily or several times a day) and weight loss (none, <5kg, 5-10kg, >10kg) were each scored on a 0-3 scale (Eckardt score). Chest pain was scored on a 0-4 scale (none, < monthly, monthly, weekly, daily). The effects of dysphagia (at least daily), regurgitation (at least daily) and chest pain (at least weekly) on the SF-36 scores were investigated. Differences were tested by the Kruskal-Wallis test and Mann-Whitney test. A p-value < 0.003 was considered significant (Bonferroni). 113 (85%) of 135 patients (mean age 51.8 years (20-91), 52.7% men) responded. Two patients were excluded because of a language barrier and one because of nasogastric feeding. The total group of achalasia patients scored lower than HC on all the SF-36 subscale scores, except mental health and health change (all p<0.001). 43.5% and 12% experienced at least daily dysphagia and regurgitation, respectively. Achalasia patients with at least daily dysphagia scored lower on general health experience (p=0.003) than those without. At least weekly chest pain was reported by 36.4% of the achalasia patients. This subgroup of achalasia patients scored lower than those without on the scales social functioning, physical role limitation and pain (p=0.002, p=0.003 and p<0.001, resp). Regurgitation and weight loss did not affect HRQoL. Conclusion: HRQoL is markedly decreased in treated achalasia patients and the presence of chest pain seems to play a major role in this.

Measuring the severity of upper gastrointestinal complaints: does assessment correspond between general practitioner and patient?

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Objective: The severity of upper gastrointestinal (GI) complaints is often measured by questionnaire, in some studies used to guide an interview by a physician, in other studies they are used in a self-administered way. The results of all these different studies using different manners to measure GI complaints are often compared, but little is known about the interrater agreement. Therefore, the aim of this study was to investigate the interrater agreement between physician and patient concerning the severity of the patients upper GI complaints.Method: Patients (N=316) with upper GI complaints treated with esomeprazole by their general practitioner (GP) were registered. Patient and GP scored the severity of the 8 GI complaints on a 7-point Likert scale before and after treatment. Only patient questionnaires filled out within 2 days after the visit were included to make sure that treatment effects or natural course did not interfere. Weighted kappa and mean differences between the patient and physician scores were calculated.Results: The weighted kappas ranged from 0.14 to 0.68 indicating a poor to moderate agreement between GP and patient on the severity of the studied symptoms. The mean differences between the GP scores and patient scores were very low for all symptoms indicating that GPs as frequently overestimate as underestimate the severity. However, at baseline, GPs more often underestimate the severity of lower abdominal pain and vomiting (mean differences 0.27 (95%CI 0.15-0.39) and 0.13 (0.04-0.23) resp.). At follow-up, the severity of belching, upper and lower abdominal pain, nausea and early satiety (mean differences: 0.20 (0.09-0.31); 0.20 (0.10-0.29); 0.18 (0.10-0.25); 0.13 (0.05-0.20); 0.27 (0.15-0.39) resp.) was more often underestimated by the GP. The treatment effect was overestimated by the GPs for belching and lower abdominal pain (mean differences 0.29 (0.09-0.48) and 0.35 (0.13-0.57) resp.) and underestimated for nausea (mean difference 0.41 (0.12-0.70)).
Conclusion: The agreement between GP and patient is low. Consequently, results from studies using self-reported GI symptom questionnaires can not easily be compared with studies using interviews by physicians.

Environmental risk factors for cancer development are not different between patients with esophageal and gastric cardia adenocarcinoma

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Over the past 3 decades, the major subtype of esophageal carcinomas has shifted from squamous cell carcinomas (SCC) to adenocarcinomas (EAC). This change in incidence is attributed to differences in etiology. However, it is largely unknown whether the same or different risk factors for cancer development are present in patients with EAC and gastric cardia adenocarcinoma (GCA).The aim of this study was to compare environmental risk factors between patients with SCC and EAC on the one hand and patients with EAC and GCA on the other hand. Between August 2002 and November 2005, all patients who were evaluated in the Erasmus MC for esophageal or gastric cardia cancer by endoscopic ultrasonography were asked to fill out a questionnaire. This questionnaire comprised information on the subjects' history of diet habits, physical activity, gastro-esophageal reflux disease, history of proton-pump inhibitors (PPIs), H2-receptor antagonists (H2RAs) and NSAID/aspirin use. Chi-square tests and t-tests were used for statistical analysis. A total of 208 patients filled out the questionnaire of whom 112 patients were diagnosed with EAC (90% males, mean age±SD: 62 ± 10 yr), 42 patients with GCA (85% males, 65 ± 11 yr) and 54 patients with SCC (65% males, 63 ± 9 yr). Age, race and education were comparable between the three groups. More female patients were diagnosed with a SCC compared to EAC ($p<0.001$). Mean body mass index at age 20 years was significantly higher in EAC compared to SCC patients (24±3 vs. 22±3 kg/m2, $p<0.001$) but did not differ between EAC and GCA (24±5 kg/m2, $p=0.46$). Symptoms of heartburn were more frequently present in EAC compared to SCC (50% vs. 23%, $p=0.001$) and GCA patients (31%, $p=0.031$). Use of PPIs was more common in EAC compared to SCC patients (48% vs. 30%, $p=0.04$), but did not differ between EAC and GCA patients (48% vs 38%, $p=0.27$). As compared to GCA, EAC patients more often used NSAIDs or aspirin (47% vs 29%, $p=0.036$; 51% vs 24%, $p=0.003$). No difference between EAC and SCC patients was observed in NSAID or aspirin use (47% vs 33%, $p=0.078$; 51% vs 39%, $p=0.167$). Smoking and alcohol consumption was not different between the three groups.
Conclusion: Patients with EAC and GCA do not differ grossly with regard to environmental risk factors for cancer development. In contrast, patients with EAC experienced more reflux symptoms than patients with SCC as could be expected from the etiologic sequence in development of EAC.

The COX-2 -765C -1195A haplotype predisposes for the development of esophageal adenocarcinoma

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Since COX-2 expression increases in the metaplasia-dysplasia-adenocarcinoma sequence in Barrett-esophagus, it may have a causal relationship with neoplastic progression in the esophagus. High expression levels are also associated with poor 5-year survival rates of esophageal adenocarcinoma. COX-2 is the rate-limiting enzyme for the production of prostaglandin E2 (PGE2), a compound associated with carcinogenesis in many inflammatory diseases. We aimed to determine the association between COX-2 haplotypes and esophageal carcinogenesis.DNA was obtained from 140 Caucasian patients with an adenocarcinoma of the esophagus (mean age 63±11; 91% male), 250 Caucasian patients with histologically confirmed Barrett's esophagus (mean age 62±13; 68% male) with a mean Barrett-segment length of 4.2 ± 2.3 cm, and 247 Caucasian patients with endoscopically confirmed reflux esophagitis (mean age 56±14; 53% male). COX-2 haplotypes were determined by PCR amplification of the promoter region , followed by determination of the polymorphisms at -765C/G and -1195A/G by RFLP with restriction enzymes AciI and PvuII respectivelyThe population tested, consisted of 171 (14%) CA (-765C & -1195A), 817 (66%) GA, and 258 (20%)GG haplotypes, and none of the relatively rare GC-halotype. The haploptype distribution in patients with reflux esophagitis and Barrett's esophagus was similar (CA 12%, GA, 68%, GG 21%), but differed significantly from patients with esophageal adenocarcinoma (Ca 21%, GA 58%, GG 20%), in whom the CA-haplotype was significantly more common ($p<0.0001$). Furthermore, homozygosity of CA was only observed in patients with Barrett's esophagus patients (1.6%) and esophageal adenocarcinoma (5.0%) ($p=0.002$). CA-carriership was strongly associated with an increased risk for esophageal adenocarcinoma (OR 1.94; 95%CI 1.23-3.08; $p=0.005$), and homozygosity for the CA-allele was associated with an even greater risk (OR 3.83; 95%CI 1.09- 13.84; $p=0.036$). Conclusion: The COX-2 CA-haplotype is associated with an increased risk for the development of esophageal adenocarcinoma in Barrett's esophagus and reflux esophagitis patients. As the COX-2 CA-haplotype has been demonstrated to be associated with increased levels of PGE2, PGE2 seems to be involved in esophageal carcinogenesis in patients with a Barrett's esophagus and reflux esophagitis.

Comparison of conventional techniques and FLIP for the determination of OGJ characteristics in GERD patients pre and post laparoscopic Nissen fundoplication

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Background & Aims: Insight in the competence of the esophagogastric junction (EGJ) is important to the understanding of gastroesophageal reflux disease (GERD). No routine method is available to assess the compliance of the esophagogastric junction. A functional lumen imaging probe (FLIP) was constructed to measure eight cross sectional areas (csa) at 4mm intervals inside a saline-filled bag using impedance planimetry and containing two pressure side holes. We assessed the compliance of the OGJ in untreated GERD patients and in patients who had a laparoscopic Nissen fundoplication compared to healthy volunteers (HV) and compared these results with conventional manometry and pH metry.
Methods: 5 GERD patients (57 (43-67), 3M), 4 post Nissen patients (54 (43-60), 3M) and 5 HV (40 (20-58), 3M) were evaluated. They underwent a compliance measurement using the FLIP, esophageal manometry and 24 hrs pH metry. The FLIP was positioned with the bag straddling the EGJ using manometry readings and point of respiratory inversion as a guide. The bag was filled with saline at a rate volume of 25 ml/min to a maximum of 60 ml. Bag pressure and csa were recorded. A pH below 4 > 5.78% of total time was considered to be pathological. For statistical analysis, unpaired Student's t-tests were used and data is presented as mean ± SE.
Results: GERD patients have significant more pathological acid reflux 5 cm above the LES compared to patients after a Nissen and healthy volunteers (GERD patients 10.5 ± 3.2 vs post Nissens 0.7 ± 0.4 vs HV 2.3 ± 0.7 ($P<0.031$)). Manometric results did not differ between groups (basal LESp: GERD patients 6 ± 2 mmHg; post Nissens 8 ± 3 mmHg; HV 9 ± 3 mmHg (NS)). At a bag pressure of 7 mmHg during distension the average diameter of the EGJ in GERD patients and HV was 13mm while the post Nissen average diameter at this pressure was 7mm. However, at 13 mmHg in healthy controls the diameter remained about 13mm whereas GERD patients have an average diameter of 22mm and post Nissens a diameter of 8mm.
Conclusion: FLIP studies showed a greater distensibility in GERD patients compared to HV and post Nissens and may offer a direct method to assess changes in compliance of the EGJ after a lap Nissen. Further studies are needed to confirm these findings.

Characterisation of Intraluminal Impedance Patterns Associated with Gas Reflux (Belching) in Healthy Volunteers *

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Multichannel Intraluminal Impedance(MII) recording allows assessment of flow through the esophagus and differentiation between liquid and gas contents. MII criteria have been developed for recognition of gas but have not been validated during known gas reflux in humans. The aim of this study was to characterize patterns of impedance change associated with gas reflux and to examine the interrelationships between the magnitude of impedance change, luminal diameter and electrode-mucosa contact. We studied 10 healthy volunteers(6M:4F, 21-37yrs) using an esophageal MII-manometry catheter. After catheter placement, subjects were asked to drink up to 600ml of carbonated softdrink. Belching episodes were then recorded for 20min and the protocol was repeated. Only belches confirmed by transient LES relaxation and associated with an esophageal common cavity episode were included for analysis. A further 5 subjects(3M:2F, 26-52yr) underwent simultaneous MII and videofluoroscopy(VF) during performance of the same protocol. 'Standard' MII criteria for recognition of gas reflux were a retrograde or synchronous impedance rise of ≥50% in ≥2 channels that exceeded 5kΩ in ≥ 1 channel. VF was analysed blinded from MII results and vice versa. All analysed belches (n=88) were associated with a pattern of impedance rise which was either retrograde(62.5%), synchronous(19.3%) or antegrade(18.2%). Median(IQR) impedance at the onset and peak of gas reflux was 2.0(1.6, 2.7)kΩ and 4.4(2.8, 7.5)kΩ respectively and the median % increase was 106.6%(50.2, 200.3). Of all belches 31(35.2%) did not meet the 'standard' MII criteria because the impedance rise was antegrade(18.2%), did not increase by ≥50% in ≥2 channels(9.1%) or did not exceed 5kΩ in any channel(23.8%). During MII-VF 15 belches were recorded. The magnitude of impedance change increased with increasing luminal diameter during gas reflux($r=0.718$, $p<0.0001$). The magnitude of impedance change was greater when electrodes were not in direct contact with the esophageal mucosa(7.0(5.4, 7.8)kΩ) compared to when one(2.4 (1.1, 5.2)kΩ, $p<0.001$) or two(1.8 (0.8, 2.6)kΩ, $p<0.001$) electrodes were.
Conclusion: A significant number of gas reflux episodes do not meet current standard impedance-based criteria for their recognition. Factors including the degree of esophageal distension as well as the extent of direct contact between the esophageal mucosa and MII-electrodes influence the magnitude and patterning of impedance change recorded.

Gene therapy in experimental models of esophageal carcinoma
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Barrett's esophagus and esophageal cancer are complex diseases, which require a multidisciplinary approach for its research and clinical management. In the current studies we explored the potential of gene therapy in the management of these diseases. We have focused on adenoviral gene delivery in different experimental models of esophageal carcinomas and Barrett's esophagus.In a first study we studied adenoviral gene transfer in primary single cells extracted from esophageal cancer resection specimens by collagenase treatment. With a double staining flowcytometry, fibroblasts could be differentiated from the cancerous cells and this allowed studying tumor cell specific transduction of the adenovirus. In this model the re-targeted adenovirus had a significantly better transduction in tumor cells. For a clinical more relevant model we studied whole tissue. Biopsies obtained from patients with a Barrett's esophagus or esophageal cancer, were cultured and transduced with different adenoviral vectors. Viability of the biopsies appeared to be a limiting factor in this system and the use of 95% oxygen appeared to be essential to improve it. Adenoviral transduction in these models was limited and mainly localized in stromal cells. The use of a re-targeted virus did not improve transduction, in contrast to its results in established cell lines. Potentially, gene therapy could be used for patients with a Barrett's esophagus, especially in the setting of high grade dysplasia. We used Caco-2 cells as an in vitro model and rat intestinal loops and a Barrett's esophagus rat model were used as in vivo models. In the Caco-2 cells we observed a significantly decreased adenoviral transduction upon differentiation and additive agents like acetylcysteine and DEAE-dextran could improve it. In the rat intestinal loops transduction was very limited too, but in contrast to the in vitro setting, this could not be improved with any of the additive agents. Also in the Barrett's esophagus the adenoviral transduction was limited and not localized in the Barrett's segment or the tumor like lesions. The adenoviruses can be classified into six species and 51 different serotypes, which all have a specific tropism. We explored the transduction efficacy of different promising serotypes in both esophageal tumor cell lines and in differentiating Caco-2 cells. Especially serotype 16 and 50 had a high transduction efficacy in the esophageal tumor cell lines. In the differentiated Caco-2 cells transduction was very poor for all serotypes, also for serotype 40. We conclude that although in vitro studies have shown promising result, in vivo the results of adenoviral gene therapy were disappointing. For this setting additional tools have to be developed in order to achieve adequate gene transfer.

Seven-day therapy with esomeprazole, amoxicillin and levofloxacin is very effective for H.pylori eradication

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Guidelines for *H. pylori* eradication advise triple therapy with a PPI, clarithromycin and amoxicillin, followed by quadruple therapy for failures. However, quadruple therapy can not be prescribed because bismuth is no longer available. Therefore, there is a pressing need for new effective therapies. Levofloxacin, a quinolon, has been suggested as a new and promising anti-*Helicobacter* agent. In this study we evaluated the effectiveness and safety of a new triple therapy combining esomeprazole, amoxicillin and levofloxacin in Dutch patients.
Between February and November 2005 consecutive *H. pylori* positive patients were treated with esomeprazole 40mg, amoxicillin 1000mg, and levofloxacin 500mg, all given twice daily for 7 days. At least 5 weeks after finishing therapy *H. pylori* status was tested again. Diagnosis of *H. pylori* infection was established either with biopsy-based tests at endoscopy or with a validated ^{13}C urea breath test (BreathID™, Oridion Systems).
Fifty *H. pylori* positive patients (mean age 54 years (SD: 16), 48% male, 33% smokers, 24% with peptic ulcer disease, 34% with PPI pre-treatment) were treated with this regimen. Of these patients, 10 had previously been treated unsuccessfully: 8 with first-line therapy with a PPI, clarithromycin, and amoxicillin, and 2 with first-line therapy as well as second-line therapy with a PPI, amoxicillin, and metronidazole. Overall, 48 patients (96%, 95%CI: 91-100%) were *H. pylori* negative after treatment. All 10 patients with previously unsuccessful first/second-line therapy were cured. Side-effects were reported by 32% of patients, but they were nearly always mild and did not lead to discontinuation of therapy in any of the patients. Diarrhoea was the most common side-effect.
Conclusion**:** This new seven-day triple therapy with esomeprazole, amoxicillin, and levofloxacin for 7 days is very effective and safe for *H. pylori* eradication, both as first-line therapy and as second-line therapy. It is a welcome addition to our therapeutic arsenal for treating *Helicobacter* infections.

Seroprevalence of Helicobacter pylori in two asymptomatic Dutch populations

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Helicobacter pylori (Hp) infection poses a potential risk for developing upper gastrointestinal disorders ranging from peptic ulcers to gastric malignancies. Hp prevalence is thought to be declining in Western countries, probably reflecting a birth cohort effect resulting from improvements in hygiene. To examine the secular trends in Hp seroprevalence in a native Dutch population and in non-Western immigrants by determining age specific Hp seroprevalence in representative groups from both populations. Plasma samples (794) were collected from native blood donors living in the South-Western Netherlands, including Rotterdam, equally divided over 5 age groups: I =18-28, II=29-38, III=39-48, IV= 49-58, and V=59-70 year. Information concerning age, gender, and geographic region was available, but no donor identity. Another 287 serum samples were collected from asymptomatic volunteers from an urban district of Rotterdam, predominantly populated by non-Western immigrants. All samples were tested for anti-Hp IgG by a commercial ELISA (Orion Diagnostica). In the native population Hp seroprevalence was overall 32% (254/794). Divided over different age groups Hp+ results were 17% (27/160) group I, 30% (47/158) group II, 33% (52/160) group III, 32% (51/158) group IV, and 49% (77/158). Logistic regression within donors reveals a higher age specific Hp prevalence compared to younger age groups ($p<0,001$): odds ratios (95% CI) are respectively 2,1 (1,22-3,57) group II, 2,4 (1,40-4,03) group III, 2,4 (1,38-4,00) group IV, and 4,7 (2,79-7,86) group V. No difference between gender was observed. In contrast, in the urban district Hp seroprevalence was significant higher in all age groups, 69% (198/287) overall ($p< 0,001$ Chi-square test). Divided over different age groups Hp+ results were 61% (35/57) group I, 72% (59/82) group II, 68% (42/62) group III, 74% (45/61) group IV, and 68% (17/25) group V. In this urban cohort no age-specific Hp prevalence, nor difference between gender was found.
Conclusions: The secular trend towards lower Hp infection rates was observed in the native Dutch population, but not in volunteers of the urban district, with many non-Western immigrants. However, both populations are living in the same region, Hp seroprevalence varies. These ethnical differences are of obvious importance to public health authorities planning interventions to lighten the burden of Hp associated disease.

Depot octreotide therapy in dumping syndrome: long term follow up

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Dumping syndrome is a serious complication that may affect up to 10% of patients after gastric surgery. The somatostatin analog octreotide (OCT) is effective in controlling early and late dumping symptoms in patients with severe dumping syndrome. Little is known however on long term follow up. Since 2000 depot octreotide (LAR) has become first choice over subcutaneous octreotide (SC). Here we report on 1) long term follow up of patients with dumping using octreotide therapy and 2) comparison of LAR vs SC. The group consists of 20 patients (age range 44-77 yr, 50% men) with invalidating dumping symptoms after gastric surgery (partial or total gastrectomy n=18, vagotomy n=2) who used octreotide for at least 6 months. They were seen at regular intervals evaluating systemic and abdominal symptoms, quality of life (GIQLI), body weight, fecal fat excretion and gallbladder ultrasound (gallstones). Results: mean follow up was 94 months (range 7-204). Three patients stopped LAR because of side effects and three patiens died from non related causes. All patients were changed from SC to LAR in 2000 or after 2000 were started on LAR. In 2005, 14 patients were still using OCT. Data are given at baseline (no therapy), 6 months LAR, and on OCT in 2005. Complete relief of symptoms at 6 months and in 2005 was 90 % and 70 % resp.for abdominal symptoms and 80% and 60% resp. for systemic symptoms. Body weight increased sign. ($p<0.05$) at 6 months LAR from 67±3 (baseline) to 71±3 kg but was not different from baseline in 2005: 69± 4 kg. Quality of life (max score 144) at 6 months was sign.($p<0.05$) increased over baseline: 88± 4 vs 74 ± 4 but not any more 2005: 75± 4. Fecal fat increased from 16±4 (baseline) to 31±6 g per 24 hr at 6 months ($p<0.05$) and was 21±5 per g per 24h in 2005(ns). During follow up gallstones had developed in 40% of patients. While on therapy seven patients preferred SC over LAR and OCT formulation was changed. Remarkably, 6 of 7 patients on SC had both early and late dumping while in group remaining on LAR only 1 had combined dumping, the 6 others had early dumping only. A discrepancy was observed between long term symptom control and quality of life.It is concluded that even on the longer term OCT therapy remains effective in controlling dumping symptoms. Patients with more severe dumping syndrome (early and late dumping) prefer the subcutaneous formulation while in patients with only early dumping the depot formulation is preferred.

Follow up of patients with carcinoid tumors: Combination of Chromogranin A and NT-proBNP

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Objective: 5HIAA is used as a standard marker in carcinoid tumors.We have evaluated the clinical impact of changing marker to Chromogranin A (CgA).
Carcinoid heart disease (CHD) occurs in 20-70 % of the patients with carcinoid tumors. We therefore evaluated whether natriuretic peptides (ANP and NT-proBNP) could be used in the diagnosis of CHD. Methods: 5HIAA was measured using an ELISA technique (DRG, Germany). CgA was determined by RIA (Cis Bio Int, France). The patient population existed of 18 males and 19 females. To establish a reference value for CgA we collected serum in 90 healthy volunteers. Results: The inter C.V. for 5HIAA was on average 25%, and for the CgA 6.5%. The reference values (95%) were 40 mmol/24hrs for 5HIAA and established as 120 µg/l for CgA. No significant difference was found in marker concentrations related to age or gender. The relation between tumor markers and 5 quality of life parameters were calculated after log transformation of the marker and using a linear model with random coefficients. Using this method it was shown that a change of 5HIAA did not correlate with any parameter but CgA changes were significantly related to 2 of them.
CHD was found in 8/32 patients (25%). All CHD patients had symptoms of the carcinoid syndrome compared to 67% of the non-CHD patients (p=0.08). All patients with CHD had elevated NT-proBNP levels. Degree of dilatation of right atrium or ventricle was significantly associated with higher levels of NT-proBNP (p=0.001 and p=0.002). Thickening of the tricuspid valve and degree of regurgitation were accompanied by significantly higher levels of both natriuretic peptides. Although not significant, a trend for a better survival was observed in patients with normal NT-proBNP values (p=0.13).
Conclusion: The CgA assay can replace the 5HIAA assay as a marker for follow up of patients with carcinoid tumors.NT-proBNP can be used as a reliable diagnostic marker for CHD. The combined measurement of CgA and NT-proBNP in carcinoid patients is recommended..

Abnormalities of the enteric nervous system, smooth muscle and interstitial cells of Cajal in children with colonic motility disorders *

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Colonic manometry studies in children with severe defecatory disorders often reveal abnormal contraction patterns. These patterns have traditionally been classified into myopathic, neuropathic or mixed types. Current study evaluates the relation between colonic manometry findings and abnormalities of the colonic enteric nervous system (ENS), smooth muscle and interstitial cells of Cajal (ICC).Colonic specimens were assessed from a cohort of children who underwent colonic manometry testing prior to surgery. The following immunohistochemistry stainings were used to identify abnormalities of the ENS: Neuron Specific Enolase, Calretinin, Neurofilament (neuronal markers), Synaptophysin (synaptic vesicles marker), Tyrosine hydroxylase (adrenergic pathway marker), S-100 (glial cell marker), GFAP (glial fibrillary acidic protein). ICC were stained with CD117 (c-kit), and smooth muscle markers were SMA (alpha actin) and MSA (gamma actin). Eight colonic specimens from 5 patients. One patient with Hirschsprung's disease had persistent symptoms of dysmotility after resection of the aganglionotic segment. Four patients had severe constipation of unknown origin. Manometry showed absence of colonic contractions in 3 colonic segments and low amplitude propagating contractions (LAPC) in 2 segments, compatible with a myogenic motility pattern. These specimens showed abnormalities of the ENS and a marked decrease or absence of ICC, but no smooth muscle abnormalities. Simultaneous contractions, indicative of a neuronal disorder were seen in 2 segments, an elevated level of GFAP positive cells, loss of ICC and normal smooth muscles were found. Minimal abnormalities, including an elevated GFAP level and reduced ICC staining were seen in a patient with severe symptoms of colonic dysmotility with normal manometry findings. In total 7/8 specimens showed elevated levels of GFAP positive cells, suggestive of neuronal damage. Conclusions: Although a myogenic pattern was observed on colonic manometry, abnormalities in ICC or the ENS, but not in smooth muscle markers were found. Loss or absence of ICC and elevated levels in GFAP were prevalent findings in pediatric colonic motility disorders, irrespective of the manometric pattern. Caution should be used when predicting the type of underlying neuromuscular disorder based on colonic manometry.

Clinical spectrum and survival in patients who presented with a Neuroendocrine tumours (NET) from 1995-2004

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Introduction: Patients with NET may represent a group of patients with variable clinical features pending on the primary, the metastatic sites and the hormonal production. Abdominal problems related to mesenteric mass and hence ischemia by occlusion of the mesenteric artery are not uncommon, and often difficult to manage.Aim of the study: to evaluate the clinical features and survival in patients with NET.Methods: the medical records of all patients referred to our hospital from 1995 through 2004 were reviewed to collect data at presentation about symptoms and signs, CT-scan and nuclear tests (OctresocanR and 131I-MIBG scintigraphy), as well as tumour markers urinary 5-HIAA (until 2002) or Chromogranin A (from 2002 onwards).Results: 199 patients (97 m + 102 f), median age 59 years (range 19-84) and the primary tumour in the small bowel (n=65), lung (n=19), colon (n=6), other sites (n=24) and unknown (n=85), among which the primary appeared to be in the small bowel during follow-up in 13. Liver metastases were present in 146 (73%), elevated 5HIAA in 116/175 (66%) and ChromograninA was elevated in 74/107 (71%). A positive bone scan was found in 21%. Mesenterial tumour was detected by CT-scan, in 55/181 (30%) at presentation and an additional 20 % during follow-up. The Octreoscan was positive in 77% and the MIBG scan in 60%. A total of 25 (13%) second primary tumours were found: in 17 patients before, 3 simultaneously and in 5 after the diagnosis of NET.The overall survival was significantly related to the level of 5-HIAA excretion and Chromogranin A. Particularly patients with ChrA exceeding 1000 had a poor survival. In patients with a negative Octreoscan (n=42) the ChromograninA level was elevated in 13 (62%) and 5 year survival was less favourable compared to those with a positive scan (40 vs 67%). In patients with bone metastases, however, survival was not significantly different from those without.Conclusion: a mesenterial mass is found in upto 50% of the patients, survival is related to the levels of chromogranin A and and bone metastases does not seem to be en indicator of poor prognosis.

Autologous Haematopoietic Stem Cell Transplantation in four Refractory Coeliacs with aberrant T-cells

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Autologous Haematopoietic Stem Cell Transplantation (ASCT) is being investigated for patients with severe refractory autoimmune disorders unresponsive to conventional therapies. Refractory Coeliac Disease with monoclonal aberrant T cells (RCD-type II) is usually unresponsive to available therapeutic regimens and carries a high risk of transition (60-80% within 5 years) into Enteropathy Associated T-cell Lymphoma (EATL). The objective of this pilot study is to assess the feasibility, safety and efficacy of high dose chemotherapy followed by ASCT in patients with RCD type II.Four patients [(3 males, 1 female, mean age 64.2 years (range 61-69 years)] with RCD-II have been transplanted. Stem cells were collected by leucopheresis after pre-treatment with granulocyte colony-stimulating factor(G-CSF). After conditioning with fludarabine and melphalan, ASCT was performed. Patients were monitored for clinical response of disease, adverse effects and haematopoietic reconstitution. All 4 patients completed the mobilization and leucopheresis procedures successfully and subsequently received conditioning and transplantation. Engraftment occurred in all of these patients. No major non-haematological toxicity nor transplant related mortality was observed. Marked improvement of clinical condition was recorded in all patients (mean follow-up 13,2 months, range 5-22 months).There was a significant reduction in the percentage of aberrant T-cells in duodenal biopsies associated with improvement in clinical wellbeing, and normalization of haematological and biochemical markers. Conclusions: High-dose chemotherapy followed by ASCT seems feasible and safe, and might result in long-term improvement of clinical condition in RCD patients with monoclonal aberrant T cells whose condition previously did not respond promptly to the available drugs, and possibly prevents or delays the development of EATL. Long term follow up and a prospective randomized study is suggested to confirm the efficacy of this therapy.

In-vitro cytotoxicity of bile acids in small intestine and colon cell lines with or without UDCA.

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Background: Intestinal tumors are regularly seen in the colon but rarely develop in the small intestine. Bile acids have long been characterized as intestinal tumor promoters. Ursodeoxycholic acid (UDCA) has been reported to reduce cytotoxicity of bile acids. The aim of this study is to describe the cytotoxicity of bile acids with and without UDCA in small intestine and colon cell lines. Methods: Three different cell lines were used in this study. Hutu-80 cells are small intestine adenocarinoma cells, differentiated Caco's are model for normal small intestinal cells and undifferentiated Caco-2 cells are colon adenocarcinoma cells.All cell-lines were treated with a standardized mixture of bile acids, cholic acid, chenodeoxycholic acid and deoxycholic acid with and without UDCA in a dilution sequence with a maximal concentration of 4 mM. Cytotoxicity curves of the different cell lines were assessed using a WST-1 assay. IC50 values were calculated from the concentration-response curves. Differences in IC50 values were compared using the Kruskal-Wallis procedure.Results: The mean IC-50 value (±SD) for the bile acid mixture alone was 92 µM (±15) for small intestine adenocarinoma cells, 123 µM (±32) for normal small intestine cells, and 300 µM (±32) for the colon adenocarcinoma cells, respectively ($p<0.01$). After addition of UDCA these values were 152 µM (±31), 167 µM (±55) and 568 µM (±42)($p<0.01$). Differences in cytotoxicity of a mixture of bile acids with and without UDCA were statistically significant in both adenocarcinoma cell lines ($p<0.01$), but not in normal small intestine cells ($p=0.28$).Conclusion: In-vitro small intestine cell lines are more sensitive to cytotoxic bile acids then the in-vitro colon cell line. Addition of UDCA caused a decrease in cytoxicity in all three cell lines. Although it remains to be reproduced in-vivo, there seems to be a chemopreventive effect of UDCA on cytotoxicity of bile acids in the small intestine and colon.

Effect of Aspirin on the Wnt/β-catenin Pathway is Mediated via Protein Phosphatase 2A

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NSAIDs show chemopreventive efficacy in colon cancer but the mechanism behind this remains unclear. Elucidating this mechanism is seen as vital to the development of new chemopreventive agents. We studied the effects of aspirin on the oncogenic Wnt/β-catenin pathway activity in colorectal cancer cell lines and observed that aspirin dose-dependently decreased the activity of this pathway, as judged by TCF-driven luciferase activity, reduced Wnt target gene expression, decreased nuclear localization of β-catenin, which were accompanied by increased phosphorylation and ubiquitination of β-catenin. Importantly, concomitantly with these effects, aspirin treatment caused increased phosphorylation of protein phosphatase 2A (PP2A), an event associated with inhibition of PP2A enzymatic activity, which was confirmed by a reduction in enzymatic PP2A activity. Moreover, this inhibition of PP2A enzymatic activity was essential for the effects of aspirin on the Wnt/β-catenin pathway as shown by transient transfection with PP2A mutants. The findings in this article provide a molecular explanation for the efficacy of aspirin in chemoprevention of colorectal cancer and shows biochemical evidence that PP2A is an important regulator of Wnt/β-catenin pathway activity in these cells.

Fur mediates iron-responsive repression of urease expression in Helicobacter hepaticus

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The murine pathogen Helicobacter hepaticus colonizes the enteric and hepatobiliary tract of rodents and causes inflammatory bowel lesions, hepatitis, gall-stones and hepatic malignancies. Urease is an environmentally regulated key-virulence factor for gastric Helicobacter species, but little is known on its role or its regulation in enterohepatic Helicobacter species like H. hepaticus. Here it is reported that urease expression and activity of H. hepaticus is iron-repressed, and this regulation is mediated by the trancriptional regulator Fur. H. hepaticus strain ATCC51449 and its isogenic fur mutant were grown both under low-iron and high-iron conditions. Gene expression was monitored by Northern hybridization, and protein expression was monitored by SDS-PAGE and Western blotting. Urease activity was measured via a colorimetric reaction representing production of ammonia.Iron-restriction of growth medium resulted in a three-fold increase in urease activity in wild-type H. hepaticus strain ATCC 51449. Using Western blotting and Northern hybridization it was demonstrated that iron-responsive regulation of urease expression was mediated at the transcriptional level. Insertional inactivation of the fur gene abolished the effect of iron-restriction, indicating that Fur is responsible for iron-responsive regulation of urease expression and activity. A direct role of Fur in urease regulation was confirmed using gel-shift and DNase footprint assays, which revealed that Fur displays metal-dependent binding to a Furbox-like sequence in the promoter region of the urease gene. Conclusions: H. hepaticus regulates its urease expression and activity in response to iron-availability via Fur, and this represents a novel type of urease regulation in bacteria, as well as a novel function for Fur in regulation of virulence determinants. Since iron-restriction is often used by pathogenic bacteria as a signal for entering the host, this suggests that this form of regulation may be required for the chronic colonization of the murine hepatobiliary tract by H. hepaticus.

Adoptive transfer of non-transgenic mesenteric lymph node cells induces colitis in athymic hla-b27 transgenic nude rats

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HLA-B27 transgenic (TG) rats develop spontaneous colitis when colonized with intestinal bacteria, whereas athymic nude *(rnu/rnu)* HLA-B27 TG rats without T cells remain disease free. Bone marrow transplant studies have implicated hematogenous cells expressing HLA B27 in the pathogenesis of this colitis. The present study was designed to determine whether or not HLA-B27 expression on T cells is required for development of colitis after transfer of mesenteric lymph node (MLN) cells into *rnu/rnu* HLA-B27 recipients. Athymic non-transgenic (non-TG) and HLA-B27 TG recipients received either TG or non-TG MLN cells from *rnu/+* heterozygous donor rats in which T cells develop normally. After eight weeks recipients were euthanized and MLN cells were collected for flow cytometry and *in vitro* stimulation with cecal bacterial lysate. Cecal and colonic tissues were collected for histologic scoring, and myeloperoxidase (MPO) and IL-1β were measured in cecal homogenates. In separate experiments, CFSE labeled cells were injected into recipients in order to detect T cell proliferation of transferred cells.
HLA-B27 TG *rnu/rnu* recipients receiving either non-TG or TG MLN cells developed severe colitis and had higher cecal MPO and IL-1β levels, and their MLN cells produced more IFN- and less IL-10 after *in vitro* stimulation with cecal bacterial lysate compared to *rnu/rnu* non-TG recipients which remained disease free after receiving either TG or non-TG cells. Interestingly, proliferating donor TG T cells were detectable one week after adoptive transfer into *rnu/rnu* TG recipients but not after transfer into non-TG recipients. Conclusions. T cells from either non-TG or TG donors induce colitis in *rnu/rnu* TG but not in non-TG rats, suggesting that activation of T cells by HLA-B27-expressing accessory cells, defined as non-T cells that either present antigen to T cells or perform co-stimula-ory functions, is pivotal to the pathogenesis of colitis in this model.

KRAS and BRAF mutations are rare in early adenomas from patients with familial adenomatous polyposis and MYH-associated polyposis.

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Introduction: KRAS and BRAF mutations frequently occur in colorectal cancer and are shown to have oncogenic capabilities. Their frequent presence in sporadic adenomas and in mismatch repair-deficient tumors has suggested the involvement of the RAS/RAF pathway at early stages of adenoma progression. Familial adenomatous polypsosis (FAP) accounts for approximately 1% of cases of colorectal cancer and arises from germline mutations of the adenomatous polyposis coli (APC) gene. In a FAP mouse model, animals with KRAS mutation have a more aggressive disease leading to an increased number of adenomas and early onset of colon carcinoma. Whether the same is true for FAP and MYH patients is at present unknown. Aim: To determine the frequency of hot-spot regions of KRAS and BRAF mutations in adenomas from patients with FAP, MAP (MYH-associated polyposis), and other polyposis syndromes without identifiable mutation.Methods: We investigated the prevalence of KRAS point mutations at codons 12,13, and 61, as well as of BRAF mutations at exon 15, in tumor cells micro-dissected from low dysplastic polyps derived from: 9 FAP patients (38 dysplastic, 14 normal areas), 4 MAP patients (18 dysplastic, 7 normal areas), and 2 patients with polyposis without genetic diagnosis (9 dysplastic, 5 normal areas). Mutation screening for KRAS and BRAF was performed by PCR amplification and direct sequencing. Results: No KRAS mutations were detected in any of the FAP and MAP samples, nor in any of the 14 samples of phenotypic FAP patients with no known germline mutation. No BRAF mutation was found in the samples of both FAP and MAP patients, while they were detected in 3 of 14 (21%) samples (all from dysplastic areas) from a polyposis patient with no known germline mutation. All 3 mutations were V599E, a previously described mutation hotspot. Conclusions: The absence of KRAS and BRAF mutations in adenoma from FAP and MAP patients suggest that activation of RAS/RAF signalling plays a minor role at early stages of polyp progression.

Association of Y chromosome haplotypes with Barrett's esophagus and Esophageal Adenocarcinoma in the Dutch Caucasian population.

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Barrett's esophagus (BE) is a metaplastic condition of the distal esophagus, which predisposes for the highly malignant esophageal adenocaricoma (EAC).It is known that BE and EAC have a 3-7 times increased incidence in males especially in the Caucasian population. Interestingly the loss of Y chromosome is one of the most consistent aberration in BE and occurs already in the stage of metaplasia and has a high frequency in dysplasia. We hypothesized that certain Y chromosome haplotypes may be associated with increased or decreased susceptibility for BE and EAC development.To test this hypothesis, we have analyzed a set of 6 Y chromosome linked polymorphisms to define 7 major Y chromosome haplotypes (A,B-C, DE, F(xJ,xK), K(xP), J, P(xR1a), R1a) in the Dutch Caucasian patients presenting with BE (n=286), EAC (n=116) and BE free Esophagitis (n=109). Their Y haplotype profile was subsequently compared with matched for age (>50 years old), BE free Controls (n=90). We found significant difference in frequencies of the P(xR1a) and DE haplotypes between the patient groups and the control population. The P(xR1a) haplotype had a significantly higher frequency in BE patients (62%) vs. Control (44%) (OR- 2.0, $p<0.001$). In contrast the frequency of the DE haplotype was significantly lower in patients with BE (3%) and EAC (1,7%) vs. Control (14,5%)(OR- 0.19, $p<0.001$ and OR-0.10, $p<0.0001$, respectively). Also the DE haplotype was lower in esophagitis (7,3%) vs. EAC (1.7%) (OR-0.22, $p<0.05$). Our results suggest that the P(xR1a) haplotype is associated with increased susceptibility for BE. In contrast the DE haplotype is associated with decreased predisposition to both BE and EAC. We postulate that haplotypes P(xR1a) and DE might be linked to the variants of genes which predispose and protect against BE /EAC development, respectively. Together with other markers, this may help identify those patients who would benefit from surveillance.

Indomethacin enhances bile salt detergent activity: relevance for NSAIDs-induced gastrointestinal mucosal injury.

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Although non-steroidal anti-inflammatory drugs (NSAIDs) are widely used, their gastroduodenal toxicity is a major drawback. Apparently, gastrointestinal toxicity is partly independent from cyclooxygenase inhibition, since COX knockout mice are not protected. Interactions between NSAIDs and intestinal bile salts may be important: those NSAIDs undergoing extensive enterohepatic circulation (e.g. indomethacin) are most likely to induce intestinal damage, and bile duct ligation prevents gastrointestinal lesions under these circumstances. Inter-mixed micellar-vesicular (non-phospholipid associated) bile salt concentrations (i.e. bile salt simple micelles and monomers: IMC) are thought to be responsible for bile salt cytotoxicity, and NSAIDs might increase bile salt content in the IMC and/or affect bile salt-phospholipid interactions. We here evaluate effects of indomethacin on bile salt cytotoxicity with complementary in vitro and ex vivo systems (bile salt-induced erythrocyte hemolysis; bile salt-induced LDH release by CaCo2 cells; electric parameters of rat colonic mucosa in Ussing chambers) and on bile salt contents and composition in the inter-mixed micellar-vesicular fraction (obtained by rapid centrifugal ultrafiltration). In the erythrocyte model, indomethacin alone did not induce hemolysis. In contrast, indomethacin enhanced and phospholipids protected against hemolysis induced by hydrophobic taurodeoxycholate (indomethacin 5 mM, TDC 0-10 mM). Whereas in absence of indomethacin, hydrophilic tauroursodeoxycholate protected against taurodeoxycholate-induced hemolysis, in presence of this NSAID, hemolysis was aggrevated. Indomethacin also increased taurodeoxycholate-induced LDH release in CaCo-2 cells and bile salt-induced rat colonic mucosal injury in Ussing chambers, and prevented potential protective effects of tauroursodeoxycholate in these systems. Indomethacin did not affect inter-mixed micellar-vesicular bile salt concentrations or compositions in representative model bile systems. Our data show that indomethacin enhances bile salt-induced cytotoxicity, without affecting inter-mixed micellar-vesicular bile salt concentrations or compositions. Indomethacin could interfere with bile salt-phospholipid interactions. These findings may be relevant for gastroduodenal injury during NSAIDs therapy.

Helicobacter pylori inhibits proliferation but not activation of T-cells

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In spite of the strong inflammatory response Helicobacter pylori infection always leads to a chronic inflammation of the gastric mucosa. The mechanisms by which this bacterium is able to overcome and survive such a response are still not fully understood. Experimental animal infection models indicate that a specific T-cell response is crucial for clearance of the infection. The aim of this study was to investigate whether H. pylori affects T-cell responsiveness. H. pylori strain J99 was grown under standard conditions. Peripheral blood mononuclear cells (PBMC) and T-cells purified by immunomagnetic selection were isolated from blood of healthy volunteers. The cells were stimulated with phytohemagglutinin (PHA) and cocultured in the presence of either no, five or ten bacteria per cell for three days. On day one the effect of H. pylori on the expression levels of the activation markers CD69 and CD25 was determined by flow cytometric analysis. The effect of H. pylori on proliferation of purified T-cells was measured on day 3 by [^{3}H]-thymidine incorporation. The effect of H. pylori on the number of cell divisions was determined on day 3 on the CD3^{+} cell fraction of PBMC by CFSE dilution.H. pylori did not inhibit the expression of activation markers CD69 and CD25 of T-cells upon stimulation of PBMC (respectively 55%±9 versus 48%±12 in the control, p= 0.11; and 44%±24 versus 34%±16 in the control, p=0.11; n=3). In contrast to these results the data of the [^{3}H]-thymidine incorporation assay showed that H. pylori inhibited the proliferation of stimulated T-cells (n=5, p=0.04) in a dose dependent way. The CFSE dye dilution assay showed a decrease in the number of cell divisions of T-cells incubated with H. pylori (3.0 versus 4.5 in the control, p=0.06, n=4), which implicates that the inhibitory effect of H. pylori on the proliferation of T-cells results from the inhibition of T-cell division. Conclusion: H. pylori does not inhibit initial activation but suppresses ongoing division of T-cells. This effect may contribute to the persistence of the bacteria in the immune competent host.

The role of the p110δ PI3-kinase isoform in inflammatory bowel disease

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The molecular mechanisms of IBD remain poorly defined. Toll-like receptors (TLR) mediate innate immune responses and are present on immune cells such as macrophages and increased cytokine production through these receptors plays a role in the pathogenesis of IBD.
PI3-kinases (PI3K) are lipid kinases that control many cellular responses. The p110δ isoform of PI3K is mainly expressed in leukocytes. Inactivation of p110δ in mice (p110δKI) leads to chronic focal colitis. This implies a role for p110δ in the pathogenesis of IBD. Also the human p110δ gene maps to the IBD7 locus.
Previous studies have shown that PI3K is a suppressor of cytokine production triggered by TLR signaling, preventing excessive innate immune responses. Here we studied the role of normal luminal flora in p110δ related colitis and of p110δ in bone marrow derived macrophages (BMDM) TLR signaling.
Colonic sections of p110δKI mice derived from conventional and specific pathogen-free (SPF) environments were stained with H&E for histological analysis.
Wild-type or KI BMDM treated with or without D030 (p110δ inhibitor) or LY294002 (PI3K inhibitor) were stimulated with LPS and cytokine production and protein phosphorylation status were assessed.
p110δKI mice from a conventional environment develop colitis at 16 weeks. Histology reveals mucosal hyperplasia, hyperplasic glands, crypt abscesses, leukocytic infiltration and focal erosion. In contrast, SPF p110δKI mice show no inflammation or other pathology in any layer of the bowel.
IL-12p40 production shows a 2-fold increase in p110δKI BMDMs. LPS induced Akt phosphorylation (indirect measure of PI3K activity) in BMDM is abrogated by LY294002 and, to lesser extent, by D030 which is in contrast to phosphorylation of IκBα, pIKKα/β, Erk and p38 which are unaffected by the inhibitors.
In conclusion, mice lacking p110δ spontaneously develop IBD only in the presence of normal luminal flora. p110δKI macrophages produce increased IL12 levels in response to LPS. LPS activates Akt/PI3K, MAP-kinase and NFκB pathways. PI3K inhibitors decrease Akt/PI3K activity but fail to inhibit the other pathways. These findings emphasize the role of p110δ in the pathogenesis of IBD, likely via TLR-dependent cytokine production. However the exact signalling pathways remain unknown.

Altered Bone Morphogenetic Protein signaling in the Helicobacter pylori infected stomach

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Morphogens regulate epithelial cell fate decisions in the adult gastrointestinal tract. We hypothesized that influx of inflammatory cells into the lamina propria may disturb the normal expression gradients of morphogens (morphogenetic landscape) in gastro-intestinal epithelia. We therefore examined changes in the activity of the Bone Morphogenetic Protein (BMP) pathway in the normal and Helicobacter (H.) pylori infected gastric mucosa. We show that BMP receptors, the activated (phosphorylated) form of the intracellular BMP signal transduction protein SMAD1 and BMP target ID2 all localize to gastric epithelial cells that are at the end of the axis of epithelial renewal in the normal mucosa. Colonization of the human gastric mucosa with H. pylori results in an increase of BMP2 expression caused by influx of inflammatory cells that produce BMP2. Furthermore whereas no BMP4 is detected in the normal antrum, focal infiltrates of BMP4 expressing cells are found in the H.pylori infected stomach. This influx of BMP expressing cells is associated with an increase in epithelial BMP signaling. Interestingly, a shift of the activity of the BMP pathway is observed towards the precursor cell compartment (isthmus) of the gastric units. Thus, H. pylori infection results in an influx of inflammatory cells that disturb the normal activity gradient of a morphogenetic pathway with an established role in epithelial cell fate regulation. Our data suggest that morphological changes in epithelial histology may result from alterations in the morphogenetic landscape secondary to changes in the cellular composition of the lamina propria.

Decreased cytotoxicity of bile after ursochol intervention in patients with familial adenomatous polyposis (FAP): a pilot study.

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Familial Adenomatous Polyposis (FAP) is an autosomal dominant disorder, which is characterized by numerous colorectal adenomas. Without prophylactic colectomy, FAP will inevitably lead to colorectal cancer at a relatively young age. Additionally, most patients with FAP have extra-colonic manifestations, and the duodenum is the main site for these (pre-) malignant manifestations. Duodenal adenomas are clustered mainly in the peri-ampullary region and bile acids are known tumour promoters. This suggests a possible role of bile in the adenoma-carcinoma sequence in the duodenum. However ursodeoxycholic acid, a tertiary bile acid, might have chemopreventive properties.The aim of this study is to investigate whether 1) ursochol is tolerated by patients with FAP, 2) it is possible to enrich the bile of these patients with ursodeoxycholic acid and 3) a difference in cytotoxicity of the bile of these patients before and after the ursochol intervention can be observed.A three-month's unblinded intervention with ursochol (25 mg/kg bodyweight) was performed in 5 patients with FAP. After intravenous administration of CCK-8, duodenal bile was collected before and after this intervention period. Concentrations of bile acids were determined by gas chromatography. Cytotoxicity was performed in three different cell lines: HT-29 (colonic adenocarcinoma cells), Hutu-80 (duodenal adenocarcinoma cells), LT-97 (FAP colonic adenoma cells) by applying the WST-1 assay. The cells were incubated with diluted bile and the dilution at which the cell survival was 50 % (IC50) was determined.Ursochol was well tolerated by all patients with FAP. The percentage of ursodeoxycholic acid in the bile increased from 0% to 49% (range 29%-59%) after the intervention period. After heat inactivating of the bile (to inactivate pancreatic enzymes), the cytotoxicity of the ursodeoxycholic acid enriched bile towards the HT-29 cells was 3-fold lower as compared to the bile before the intervention ($p = 0.04$). By using the Hutu-80 or LT-97 cells, a non-significant trend towards a decreased cytotoxicity after the ursochol intervention was shown.Patients with FAP tolerate a high dose of ursochol and their bile can be highly enriched with ursodeoxycholic acid. Furthermore, the enrichment with ursodeoxycholic acid seems to lower the cytotoxicity of this bile in vitro. A double-blinded controlled intervention with ursodeoxycholic acid in patients with FAP with duodenal adenomas seems worthwhile.

Direct access colonoscopy for general practitioners in the Netherlands is feasible and has a high diagnostic yield.

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General practitioners (GP) have a central role in the Dutch health care system. Patients can only visit hospital specialists after referral by a GP. Although GP can usually order sigmoidoscopies and gastroscopies directly, colonoscopies can only be ordered by gastroenterologists after referral to the gastroenterology outpatient clinic. We assessed the feasibility of a direct access colonoscopy (DAC) program for GP. In addition, we retrospectively analysed the diagnostic yield of a DAC. With intervals of 2-6 months five groups of GP (totalling 130 GP) were formally trained about indications, contraindications and potential complications of colonoscopies. Thereafter they were allowed to request DAC. The first 1548 DAC were analyzed. After 23 months all 130 GP were trained for the DAC-program. In 30 months 1548 DAC were performed. In this group, the mean age was 59 (range 16-91), 46.4% male. The median waiting time was 21 days (range 1-62) and did not significantly change after introduction of DAC. Indications included abdominal pain (30.1 %), rectal bleeding (32.0 %), altered bowel habits (31.6 %) and various other indications (chronic diarrhea, follow up adenoma's, hereditary cancer, anemia; all < 10%). Endoscopic findings were colorectal carcinoma (4.5%), adenomatous polyps (18.9%), hyperplastic polyps (15.1%), inflammatory bowel disease (7.1%), hemorrhoids (11.4%), diverticular disease (25.7%) and miscellaneous (0.5%). No abnormalities were found in 31.5%. Colonoscopy was incomplete in 6.5%. The main indications abdominal pain, rectal bleeding and altered bowel habits did not predict presence of significant disease. Of all patients 80,7% was referred back to the GP. Further specialist analysis and treatment was required in 19.3%: carcinoma and endoscopically irresectable polyps 5.6%, abdominal pain 3.2%, inflammatory bowel disease 2.9%, hereditary cancer syndromes 1.3%, complications of colonoscopy 0.6%, miscellaneous 5.7%.
Conclusion: Implementation of DAC for a large group of GP is feasible within a relatively short amount of time. Significant disease is found in a high proportion of DAC. DAC may reduce gastroenterologist's outpatient clinic workload and shift workload to endoscopies.

A nationwide survey evaluating adherence to guidelines for follow-up after polypectomy or treatment for colorectal cancer

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Endoscopic follow-up (FU) is thought to be important for patients treated for colorectal adenomas or cancer (CRC). In the Dutch post-polypectomy guidelines only the number of adenomas indicates the FU interval, whereas in other countries like the United States, size and grade of dysplasia of adenomas are also taken into account. Whether this remarkable difference in policy is also reflected in clinical practice, is unknown.We therefore assessed the adherence to the current Dutch post-polypectomy guidelines and those for FU after CRC resection.A survey was sent to all Gastroenterology Departments in the Netherlands. The survey consisted of 4 questions about the logistic organisation of FU in each unit, and 6 fictitious cases focusing on post-polypectomy FU intervals, including cases with different numbers, sizes, and grade of dysplasia of adenomas. Five cases focused on FU after CRC.The respons rate was 85% (64/75). Fifty-eight percent (37/64) of the GI-units applied a passive FU-policy, providing a FU advice after index endoscopy, but then leaving the responsibility for FU to patients and their general practitioners. Invitation letters for FU were sent by 42% of the units.In two fictitious query-cases with 2 large adenomas, 42% of the respondents advised FU colonoscopy at a shorter interval than the guideline-recommended 6 years interval. For a case diagnosed with a villous adenoma with high grade dysplasia, 52% of respondents advised FU within 1 year, only 22% advised FU after 6 years as was recommended in the guidelines. In a case diagnosed with 5 adenomas, 80% advised FU after 3 years, according to the guidelines. FU endoscopy after treatment for CRC was advised in 52% of the respondents at an interval shorter than the guideline-recommended 3-5 yrs.
In conclusion, passive FU-policies are still very common, likely leading to under-performance of the FU program. On the other hand, adherence to FU guidelines varies considerably, often leading to more frequent endoscopies than advised. Guideline adherence is adequate with respect to number of adenomas as single parameter. However, clinicians incorporate histology into their clinical strategy, also when guidelines advise otherwise. This means that either more education on the guideline is needed, or that the guideline needs reconsideration to meet clinical judgement. In that case, size and/or histology parameters should be implemented into the Dutch guideline as is common practice in the USA.

Tumor M2-PK and immunochemical FOBT: screening for colorectal cancer

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CRC is an important medical issue. Screening for colorectal cancer (CRC) reduces morbidity and mortality. Although biochemical fecal occult-blood testing (FOBT) is the only non-invasive screening method proven to be effective in reducing CRC mortality, the test has limited sensitivity. The ideal test for CRC screening should combine a high sensitivity with an acceptable specificity. In this respect, immunochemical FOBT performs better than biochemical tests. An alternative promising method is the determination of tumor pyruvate kinase isoenzyme type M2 (TuM2-PK) in stool samples. TuM2-PK is released by tumor cells and can be detected in body fluids and feces. Detection of TuM2-PK in feces may be a valuable new screening tool for CRC. The aim of this study was to compare the accuracy of fecal TuM2-PK test with immunochemical FOBT in patients with CRC or adenomas. Out-clinic patients above 18 years of age referred for colonoscopy were asked to provide one stool specimen. A subgroup of 123 subjects was analyzed, including 44 with invasive CRC, 35 with adenomas, and 44 matched controls with a normal colonoscopy. A commercially TuM2-PK ELISA (Schebo Biotech) was used with a cutoff level of 4 U/ml. Two immunochemical FOBT tests, Immo-care-C (CARE diagnostica) and OC-LIGHT (Eiken Chemical) were used for the qualitative detection of faecal occult blood.In subjects with CRC, the TuM2-PK test was positive in 37 of 44 (84%) patients, the Immo-care detected 40 (91%) and the OC-Light detected 41 (93%). In subjects with adenomas, the TuM2-PK test was positive in 9 of 35 (26%), the Immo-care detected 16 (46%) and the OC-Light identified 14 (40%). Specificity in subjects with negative findings on colonoscopy was 91% for the TuM2-PK test and 95% for both the Immo-care and the OC-Light.
In conclusion, the immunochemical FOBT's appear valuable and sensitive tests for screening for CRC. The TuM2-PK test does not seem to have supplemental value. None of these tests is sensitive enough for the detection of advanced adenomas.

Risk of colorectal cancer in Juvenile Polyposis

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Background: Juvenile polyposis is an autosomal dominant disorder characterized by the development in childhood of juvenile polyps primarily in the colorectum but also elsewhere in the gastrointestinal tract. Juvenile polyposis is associated with colorectal cancer, but the risk is unclear. Therefore, we determined the relative and absolute risk of colorectal cancer in juvenile polyposis patients. Methods: The study population consisted of 73 patients with juvenile polyposis contributing 1625.2 person years of follow-up. This included 35 males (738.9 person-years) and 38 females (886.3 person-years). The incidence rates of colorectal cancer in these patients with juvenile polyposis were compared with the general U.S. population through person-year analysis using SEER data with adjustment for population. Results: In juvenile polyposis patients the relative risk (RR) of colorectal cancer was 34.5 times (95% confidence limits [CL], 15.0-68.5) the general population. Similar risks were noted in both males (RR 36.2; CL, 13.0-76.8) and females (RR 30.1; CL, 3.5-103). The cumulative lifetime risk for colorectal cancer was 39.4%. The mean age of diagnosis of colorectal cancer was 40.4±10.7 (SD). Other gastrointestinal tumors were not observed in this cohort.
Conclusion: Patients with juvenile polyposis are at high relative and absolute risk for colorectal cancer. Vigilant colorectal cancer surveillance of these patients starting at younger age is imperative.

The use of genetic testing in Hereditary Non-Polyposis Colorectal Cancer families.

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Aims: Genetic testing in subjects from known HNPCC families is of considerable medical and psychological significance. Subjects with a mutation can benefit from a medical surveillance program, while subjects without a mutation are relieved from anxiety and can be dismissed from further surveillance. The aim of the present study was to determine the use of genetic testing in clinical ascertained HNPCC families with a known mutation in MSH2, MLH1 or MSH6.Methods: Data were collected from medical records and family pedigrees of patients originating from HNPCC families, who visited the department of Clinical Genetics of the Erasmus Medical Center between 1995 and August 2005. Pre-test genetic risk was defined as 100% (diagnosed with an HNPCC related tumor), 50% (first degree relative with an HNPCC related tumor or with a mutation) and 25% (parent with a 50% risk).Results: Thirty-four HNPCC families with a known mutation in MSH2 (n=10), MLH1 (n=12) and MSH6 (n=12) were included in the study. At the time of clinical ascertainment 27 of the 34 families fulfilled the Amsterdam II criteria. The 34 families consisted out of 970 living subjects (50% male) with a 100% (n=108), 50% (n=533) or 25% (n=329) pre-test genetic risk of carrying the family specific mutation. Genetic testing was used by 418 (43%) subjects, a family specific mutation was detected in 203 (49%) of them. Of the subjects with a pre-test genetic risk of 100%, 50% or 25%, respectively 76%, 53% and 16% used genetic testing ($p < 0.0001$ for 100% vs. 50% risk; $p < 0.0001$ for 100% vs. 25% risk; $p < 0.0001$ for 50% vs. 25% risk).There was a significant difference in the test rate between men (36%) and women (50%), $p < 0.0001$. This significant difference was found in the 50% pre-test genetic risk group (46% vs. 60%, $p = 0.001$), but not in the 100% (70% vs. 81%, $p = 0.2$) and 25% pre-test genetic risk group (13% vs. 20%, $p = 0.07$). Conclusions: There is interest in genetic testing in subjects from HNPCC families with a known mutation. Genetic testing is used more frequently by women, and by subjects with a higher pre-test genetic risk. However, acceptance of testing is far from complete, a considerable number of subjects refrains from genetic testing. This has implications for surveillance in order to prevent cancer. Methods for improved implementation of genetic testing should be studied and optimal testing should be used as a part of the standard medical care for subjects at risk for HNPCC.

Comparison of outcome of colonoscopic surveillance in HNPCC and ulcerative colitis

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Both patients with ulcerative colitis and HNPCC patients have an increased risk of developing colorectal cancer. The lifetime risk for HNPCC patients of developing colorectal cancer is 60-70%. In ulcerative colitis, the risk of developing colon cancer depends on the duration of the disease and increases 8-10 years after the onset of symptoms. In both HNPCC and ulcerative colitis patients, surveillance colonoscopy is recommended to detect pre-cancerous lesions or early stage cancers. These surveillance endoscopies comprise a large part of all endoscopies that are currently performed at the endoscopy department. The aim of the study was to compare the outcome of surveillance of these two high-risk groups. Data were derived from the Dutch HNPCC registry and from a large hospital database of ulcerative colitis patients. HNPCC patients were included if they were carrier of an MMR-gene mutation or first-degree relative of a mutation carrier, and if they had an intact colon at the time of the first surveillance colonoscopy. Ulcerative colitis patients were included if they had at least left-sided colitis, the diagnosis was proven by pathological examination of colon samples, and if they had an intact colon eight years after the onset of symptoms. The HNPCC group included 883 patients and the ulcerative colitis group 310 patients.At the first surveillance colonoscopy, 13 colorectal cancers were detected in the HNPCC group compared to no cancers in the ulcerative colitis group. In the 711 HNPCC-patients who underwent more than one colonoscopy, 54 colorectal cancers (7,6%) were detected during a mean follow-up period of 85 months. In the ulcerative colitis group, 237 patients had more than one surveillance endoscopy. During a mean follow-up period of 144 months, 11 patients (4,6%) developed colorectal cancer. In the HNPCC patient group, 82% of all detected colorectal cancers were at an early stage (i.e. Dukes A or B), whereas in the ulcerative colitis group this percentage was only 64%.Conclusion: During surveillance colonoscopy, more colorectal cancers were detected in a shorter follow-up period in the HNPCC group compared to the ulcerative colitis group. In the HNPCC patients, only 18% of the cancers were at an advanced stage compared to 36% of the tumours in the ulcerative colitis patients.

Array-based genetic evaluation of adenocarcinomas and dysplastic lesions (DALM) in ulcerative colitis

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Introduction: Longstanding ulcerative colitis (UC) is associated with a high risk of developing UC-related colonic adenocarcinoma (UCC). These carcinomas originate from dysplastic regions referred to as Dysplasia Associated Lesion or Mass (DALM). Currently it is hypothesized that chronic inflammatory conditions in the colon result in local genetic alterations that favour carcinogenesis. In contrast, sporadic colon carcinomas (SCC) which most often originate from adenomatous polyps are thought to develop from primary genetic alterations. Studies of chromosomal alterations in SCC have been helpful in the identification of genes important in their pathogenesis. AimTo evaluate chromosomal alterations in DALM and UCCMethodsWe evaluated the genomic spectra of 13 DALM/ UCC's by array comparative genomic hybridization (aCGH) with a 3500-element BAC-PAC array. ResultsSeven tumors comprised early TNM stages (2 stage 0 (c.i.s.), 5 stage I), six neoplasms were late stages (5 stage III, 1 stage IV). Frequent losses of array clones (>20% of tumors) were detected at chromosome arms 4p, 5q, and 18q, frequent gains of array clones (>20% of tumors) were found at 1q, 5p, 6p, 7p, 7q, 8p, 8q, 11p, 11q, 12q, 14q, 17q, 19q, 20p and 20q. The pattern of alterations is dominated by gains on 5p and 20q with loss of 4p, all of which were already present in a patient with carcinoma in situ. However, gain of BAC clone RP11-150P21 at 8q22.3 was found more frequently in the late-stage sub-group (P= 0.02). The distribution of gains and losses in DALM/ UCC is different from SCC, which is typically characterized by gains of whole chromosomes 7 and 13, gain on 20q, and loss on 17p and 18q. UCC's display profound genomic instability with multiple genetic abnormalities. Furthermore, the genomic changes underlying UCC differ from those seen in SCC supporting an alternative genetic pathway in the carcinogenesis of DALM and UC-associated adenocarcinomas. ConclusionChromosomal alterations in DALM/UCC are partly different from those previously described in SCC. This study supports the hypothesis that carcinogenesis of DALM involves an alternative pathway.

Relevance of small gallbladder stones, good gallbladder motility and fast crystallization in the pathogenesis of acute biliary pancreatitis, and efficacy of UDCA on biliary colics and complications in symptomatic gallstone patients awaiting cholecystectomy. (Final report Maag Lever Darm Stichting projectno. WS 00-08)

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Acute pancreatitis is a severe complication of gallstones, with considerable mortality. We explored potential risk factors for biliary pancreatitis. We compared postprandial gallbladder motility, and after subsequent cholecystectomy, numbers, sizes and types of gallstones, gallbladder bile composition and cholesterol crystallization in 21 gallstone patients with previous pancreatitis and 30 patients with uncomplicated symptomatic gallstones. Gallbladder motility was stronger in pancreatitis patients than in patients with uncomplicated symptomatic gallstones. Pancreatitis patients had more often sludge (41% *vs* 13%, $P = 0.03$), smaller and more gallstones than those with symptomatic gallstones. Also, crystallization occurred much faster in bile of pancreatitis patients (1.0 *vs* 2.5, $P < 0.001$), possibly due to higher mucin concentrations.
Although ursodeoxycholic acid (UDCA) and impaired gallbladder motility are claimed to reduce biliary pain and acute cholecystitis in gallstone patients, prospective data are lacking. We conducted a RCT on effects of UDCA in 177 symptomatic gallstone patients scheduled for cholecystectomy. Patients were stratified for colic number in the preceding year (< 3 *vs.* ≥ 3). Baseline postprandial gallbladder motility was measured in 126 patients. 26% of patients receiving UDCA and 33% receiving placebo remained colic-free during the waiting period before cholecystectomy (P = NS). Low numbers of prior colics were associated with higher likelihood to remain colic-free (59% *vs.* 23%, $P < 0.001$), without effects on complication risk. In patients evaluated for gallbladder motility, 57% were weak and 43% were strong contractors (minimal gallbladder volume > *vs.* ≤ 6 mL). In weak contractors, UDCA decreased likelihood to remain colic-free (21% *vs.* 47%, $P = 0.02$). In the placebo group, 3 pre-operative, and 2 post-cholecystectomy complications occurred. In contrast, all 4 complications in the UDCA group occurred after cholecystectomy.
In conclusion, patients with small gallbladder stones and/or preserved gallbladder motility are at increased risk of pancreatitis. Also, UDCA does not reduce biliary symptoms in symptomatic patients. Early cholecystectomy appears warranted in symptomatic gallstone patients.

Identification and characterization of proteins involved in intestinal cholesterol absorption (final report Maag Lever Darm Stichting projectno. WS 00-46)

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Human beings absorb about 1 gram of cholesterol per day. About 300 mg is derived from food the remainder is secreted by the liver and arrives in the intestine via the bile. It has long been assumed that intestinal cholesterol absorption was a passive process. Cholesterol solubilized in mixed micelles was supposed to pass the unstirred water layer followed by diffusion into the enterocyte. The last few years it has become clear that a number of transport proteins are involved in the process. At the basolateral side of the enterocyte ABCA1 mediates part of cholesterol secretion. Interestingly, at the luminal site of the enterocyte both import and export transport systems have been defined. The ABC transporters ABCG5 and ABCG8 are involved in cholesterol export while the Niemann-Pick 1-like protein 1 plays an important role in cholesterol import. This seemingly wasteful futile cycle may provide the enterocyte with a very sensitive regulatory loop. ABCG5-ABCG8 act as a heterodimer and are also involved in secretion of cholesterol from the hepatocyte into the bile. In Abcg8 knock-out mice biliary cholesterol secretion was about 80% reduced. When infused with hydrophobic bile salts these mice developed cholestasis suggesting that the absence of Abcg5/Abcg8 renders the canalicular membrane sensitive to the detergent action of bile salts. The mechanism by which these proteins mediate cholesterol transport was further investigated in cultured gallbladder epithelial cells stably expressing the transporters. The proteins donate cholesterol only to bile salt micelles preferably mixed with phospholipid. Other conventional cholesterol acceptors such as apolipoprotein A-I, HDL or phospholipid vesicles were not able to interact with Abcg5/Abcg8. Since the ABCG5/ABCG8 heterodimer is strongly expressed in the small intestine, mixed micelles can efficiently take up cholesterol from the enterocyte and so accomplish direct transintestinal cholesterol secretion. The elucidation of this novel pathway for cholesterol excretion enables development of new strategies to increase fecal removal of cholesterol.

MR Enteroclysis in Celiac disease, Refractory Celiac disease and Enteropathy associated T-cell lymphoma

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Celiac disease (CD) is generally considered a premalignant condition. Although small-intestine biopsy is mandatory an accurate radiologic examination is important to exclude complicating lesions, including intussusception, ulcerative jejunitis and lymphoma. Purpose: Aim of this study was to evaluate the abnormalities on MR enteroclysis (MRE) and to differentiate between patients with uncomplicated CD, refractory celiac disease (RCD I & II) and enteropathy associated T-cell lymphoma (EATL).In a 15 month period from September 2004, 29 patients with clinically and histologically proven CD were scanned on the 1.5 Tesla Sonata MRI scanner (Siemens Germany). EATL was diagnosed according histology and RCD according monoclonality and aberrant intra-epithelial T-cells. Patients were positioned in prone position after introduction of a nasoduodenal catheter. Methylcellulose solution (0.5%) was administered at a rate of 80-120 ml/min. Fast T1 and T2 weighted imaging (Haste and Truefisp) was used. After Glucagon and gadolinium injection, 3D gradient echo technique was used (Vibe). Two radiologists analysed two groups of patients: 14 patients (group 1) with CD (7) and RCD I (7), 15 patients (group 2) with RCD II (8) and EATL (7). Results: 17 women and 12 men with mean age of 55 years were scored. Mean age in group 1 was lower than in group 2 (47 versus 62 years, p=s). Mean splenic volume in group 1 was 226 cm3 versus 149 cm3 in group 2 (p=s) Jejuno-ileal fold pattern reversal could be noted in 9/29 patients. Intussusception was seen in 4/29 patients. Bowel wall thickening (>3mm) in 4/14 (29% group 1) versus 8/15 (53% group 2). Infiltration of mesenterial fat in 17% (2/14) in group 1 versus 67% (10/15) in group 2 (p=s). Ascites was seen in 1 patient in group 2 Lymph node enlargement (>1cm) 3/14 versus 2/15 and an increased number of nodes were seen in both groups (8/14 versus 10/15). The combination of a low splenic volume (<166cm3), bowel wall thickening (>3mm) and mesenterial fat infiltration was highly significant for predicting RCDII and EATL (p=0.004)Conclusion: CD, RCD and EATL patients showed classic signs of celiac disease on MRE Though small groups were analysed, mean age was lower and mean splenic volume was higher in CD and RCD I patients. Mesenterial fat infiltration, low splenic volume and bowel wall thickening combined are significant diagnostic signs of RCD II and EATL. Therefore MRE cannot only identify CD but also its (malignant) complications.

Tacrolimus enema treatment for left-sided colitis:a safety study

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Introduction: Systemic treatment with tacrolimus is effective in the treatment of inflammatory bowel diseases (IBD), both ulcerative colitis and Crohn's disease. However, this type of systemic treatment can be associated with severe side-effects, such as liver- and renal function disoders, insulin hyposensitivity, hypertension and myelosuppression. Topical application of tacrolimus is effective in dermatological disorders.Aim: to investigate the safety of local –intestinal- application of tacrolimus in patients with left-sided colitis.
Materials & Methods: Patients with left-sided colitis refractory to local steroid treatment or systemic steroid-, azathioprine- or cyclosporin treatment were treated with one tacrolimus enema daily for four weeks. An enema contained 2 or 4 mg of tacrolimus in a 150 ml aqueous solution. Tacrolimus whole blood trough levels (24 h after application of the enema) were measured weekly. Bloodcounts, liver enzyme tests, renal function tests, glucose, CRP and blood pressure were determined prior to, halfway and at the end of the treatment period. Finally, endoscopic assesement was performed and Disease Activity Index (DAI) was determined prior to and after the treatment period.
Results: Eight patients were included in the study. One patient refused to continue the study-medication halfway the treatment period. None of the patients reported adverse effects or showed any laboratory function disorders during or after treatment with the tacrolimus enemas. Furthermore, through levels did not exceed 4.2 ng/ml in patients either receiving 2 mg (n = 4) or 4 mg (n = 2) -enemas/day. These levels are not associated with profuse systemic immunosuppression. Preliminary assessment of the efficacy of tacrolimus enemas revealed that patients who were refractory to at least three immunomodulatory therapies (5-ASA, steroids, methotrexate, azathioprine, ciclosporin, infliximab) (n = 5) also showed no improvement of DAI on treatment with tacrolimus-enema treatment after 4 weeks. However, two patients who had been treated with a single or double immunomodulatory therapy appeared to respond well to tacrolimus enemas. One patient showed an improvement of DAI of 10 points to 2 and another patient showed improvement from 4 to 0 points.
Conclusion: Tacrolimus enemas 2 or 4 mg seem to be a safe therapeutic option for left-sided colitis. None of the patients developed side-effects, laboratory function disorders or tacrolimus whole blood levels

Azathioprine maintains first remission in newly diagnosed pediatric Crohn's disease *

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6-Mercaptopurine has been shown to spare corticosteroid use and to maintain remission in pediatric Crohn's disease (CD). We evaluated retrospectively to what extent azathioprine (AZA), the pro-drug of 6-mercaptopurine, was used in newly diagnosed pediatric CD patients and its relation to maintenance of remission. We reviewed from 3 pediatric centers the data of children with newly diagnosed CD (period 1998 – 2003, follow-up > 18 months). Two definitions of active disease (initial or relapse) were used: Pediatric Crohn's Disease Activity Index (PCDAI) > 10, or systemic corticosteroid use. Remission was defined as PCDAI ≤ 10 without use of corticosteroids. Treatments were compared with respect to initial therapy, duration and severity of active disease, and maintenance of first remission. 88 children (55M/33F, age 12±3 yr., mean±SD) were included. Only 2 patients received AZA within 1 month after diagnosis. During the first period of active disease, 33 patients received AZA (38%), while at the end of the follow-up period (38±17 mo.) 72 patients (82%) had been prescribed AZA. In patients diagnosed after 2000, AZA was prescribed at 233 days after diagnosis, compared with 686 days in patients diagnosed between 1998-2000 (median values, $p<0.05$). At initial presentation, a larger fraction of AZA patients had moderate-severe disease activity (AZA vs. non-AZA: 75% vs. 52%; $p<0.05$) and were prescribed corticosteroids (89% vs. 58%; $p<0.005$). Initial therapy with respect to aminosalicylates (~85%) and enteral nutrition (~27%) did not differ in AZA and non-AZA patients. The first period of active disease, according to corticosteroid use, was longer in AZA patients (232 vs. 168 days; $p<0.005$). In patients who had used corticosteroids during initial disease activity, the median maintenance of the first remission in AZA patients was 544 days (PCDAI) or 575 days (corticosteroid-free) compared with 254 ($p=0.08$) and 259 days ($p<0.05$) in non-AZA patients, respectively. In 12 months after reaching the first remission, a profoundly larger fraction of AZA patients had maintained a corticosteroid-free period, compared to non-AZA patients (15/26 vs. 8/28; $p<0.05$). This study demonstrates a beneficial effect of AZA in pediatric CD with respect to maintenance of first remission. AZA therapy has become more frequently used for pediatric CD, but its initiation within one month after diagnosis is still rare. Our data support a more prominent role for AZA therapy in pediatric CD.

Regional differences of several bacterial species in the non-diseased human colon

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Introduction 16S rRNA sequence information is now widely used for culture-independent detection of bacterial groups by means of QPCR. However, the knowledge of the phylogenetic position of a bacterium and its occurrence in a faecal sample does not generate information about bacterial location. This study aimed to quantitate several bacterial species in different regions of the healthy human colon.
Methods: 18 patients with macroscopic and pathohistologic non-diseased colon were included. Mucosal biopsy specimens were harvested from rectum, sigmoid colon, splenic flexure, hepatic flexure, and ascending colon. Biopsies were washed with dithioerythritol (DTT) or Phosphate buffered saline (PBS). Bacterial DNA was extracted with the DNeasy™ Tissue Kit for qPCR (Taqman). Primers and probes were based on 16S rDNA sequences for E.coli, B. Vulgatus, E. Faecalis and S. Cerevisiea. Both biopsies as well as supernatants were studied.
Results: The numbers of the E.coli and B. vulgatus are constant and comparable numbers from colon ascendens to rectum, however the numbers of E. faecalis and S. cerevisiea over the regions are too small and unequal for proper statistical analyses. We found no significance difference between the numbers of bacteria in PBS-washing as compared with DTT-washing (P=0.15). E.coli and B.vulgatus do not have regional differences in the of the microflora respectively (P=0.19 and P=0.21). The numbers of the E. faecalis and S. cerevisiea vary due to a high number of negative samples. Bacterial diversity in different regions of the colon differs between patients although there is a slight increase in numbers E. coli from ascending colon to rectum.
Conclusion: Overall, there is no regional differences found for E.coli and B.vulgatus in healthy individuals from ascending colon to rectum. The both supernatants contains more bacteria in comparing with the mucosal biopsies. There is no difference in numbers of bacteria in both washing methods respectively DTT versus PBS.

The role of colonoscopic biopsy in distinguishing Crohn's disease and intestinal tuberculosis

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Background: The histologic differential diagnosis of Crohn's disease and intestinal tuberculosis can be very challenging since both are chronic granulomatous disorders with overlapping histologic features.
Aims: To evaluate selected clinical and histologic parameters in colonic biopsies for their ability to discriminate between Crohn's disease and intestinal tuberculosis. *Methods*– Twenty five patients with Crohn's disease and 18 patients with intestinal tuberculosis were selected for this study based on established clinical, radiologic and histologic criteria. Clinical data and selected histologic parameters in colonoscopic biopsy specimens were assessed retrospectively. A total of 103 and 41 biopsy sites were evaluated in patients with Crohn's disease and intestinal tuberculosis, respectively. Results: Clinical parameters helpful in differentiating Crohn's disease from intestinal tuberculosis included chest radiographic features of tuberculosis (0% versus 56%, respectively), perianal fistulae (40% versus 0%, respectively) and extraintestinal manifestations of Crohn's disease (40% versus 0%, respectively). Histopathologic features that appeared to reliably differentiate between intestinal tuberculosis and Crohn's disease included confluent granulomas, $\geq$10 granulomas per biopsy site and caseous necrosis (present in biopsies of 50%, 33% and 22% of patients with intestinal tuberculosis patients, respectively, versus 0% of patients with Crohn's disease). Features that were far more frequent in patients with intestinal tuberculosis than with Crohn's disease included granulomas exceeding 0.05mm^2 (67% versus 8% respectively), ulcers lined by conglomerate epithelioid histiocytes (61% versus 8% respectively) and disproportionate submucosal inflammation (67% versus 10% respectively).
Conclusion: Clinical features and selected histologic parameters in colonoscopic biopsy specimens can assist in the distinction between Crohn's disease and intestinal tuberculosis.

Adherence to surveillance guidelines for dysplasia and colorectal carcinoma in ulcerative and Crohn's colitis patients in the Netherlands.

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The risk of colorectal carcinoma is increased in patients with ulcerative and Crohn's colitis. Although it has not been proven, it is generally accepted that endoscopic screening for colonic carcinoma in this high-risk population is beneficial. Surveillance guidelines have been published (e.g. AGA), but it is not known whether these are followed in clinical practice. A questionnaire was sent to all GE's in the Netherlands. Attention was particularly focussed on indications for screening, biopsy protocols and time intervals. 153 out of 244 GE's responded (response rate 63%). 5% of the respondents did not screen IBD patients. Of the remaining GE's, all screen, ulcerative colitis patients (100%), while only 65% also screen Crohn's colitis. The AGA guidelines were followed by 27%, while 27% and 46 % followed their local hospital protocol or no specific protocol, respectively. The screening was started 8-10 years (53%) after the diagnosis in case of a pancolitis and or 10-15 years later (44%) in case of a left sided colitis. Patients were screened if they had at least a proctitis (7%), left-sided colitis (67%), or a pancolitis (26%). Screening behaviour was influenced by age, co-morbidity, a diagnosis of primary sclerosing cholangitis and a positive family history of colorectal cancer as factors. Although the AGA recommends a 4-quadrant biopsy protocol every 10 cm (30-40 biopsies in total), only 43% follow this routinely, while 50% of the GE's only took 2 to 4 biopsies per segment. This resulted in less than 30 biopsies per colonoscopy in 73% of the GE's. The GE's also commented on the management after diagnosis of different forms of dysplasia. The colectomy referral rates for respectively low grade dysplasia, high grade dysplasia, DALM were 31%, 68%, and 58%, respectively.Nearly all Dutch GE's screen ulcerative colitis patients and 64% screen Crohn's colitis patients for dysplasia and colonic carcinoma, but most of them do not follow the recommended guidelines. We suspect this deviation from the guidelines to be a general phenomenon in clinical practice and not only to be restricted to the Netherlands. This practice leads to a decreased sensitivity for dysplasia, rendering screening for colorectal cancer or dysplasia in this population highly ineffective.

First European database of pediatric inflammatory bowel disease (IBD)*

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Background: Pediatric inflammatory bowel disease has a different phenotype compared to the disease in adults. For this reason, children deserve a distinctive diagnostic work-up, as described in recent guidelines. With low incidence numbers, a collaborative effort is needed to understand the phenotype of early onset IBD.
Aim: To describe a European cohort of children with newly-diagnosed IBD: Crohn's disease (CD), ulcerative colitis (UC) and indeterminate colitis (IC), and to audit compliance to European guidelines for diagnostic work-up.Methods: A collaborative prospective registry of new IBD patients (aged below 18 years) diagnosed in 30 centres in 12 European countries between May 04-May 05 was initiated. A computerized datasheet was used to record demographics, height, weight, family history, symptoms, type and location of disease, and diagnostic work-up. Results: During the 12 month study, 379 patients were reported: CD, 62% (mean age 12.0 yrs), UC 29% (mean age 11.5 yrs), IC 9% (mean age 10.0 yrs). Almost 10% had a first degree relative with IBD. Reasons for suspicion for IBD were gastrointestinal symptoms in 97% of the patients, growth failure or pubertal delay in 15%. In CD, perianal disease was found in 31.1%, perianal fistula in 9.8%. Disease complications such as abscess, stenosis or internal fistula were reported in 8.9%, 18.3% and 4.6% respectively. In UC patients, abscess was reported in 1.8% and perianal disease in 5.5%. In the whole cohort, colonoscopy had been performed in 98.4% of patients, with terminal ileum intubation in 58.5%, upper endoscopy in 82.3%, and small bowel radiology in 61.5%. In CD, disease was located (by endoscopy and/or histology) in the upper GI tract in 68%, in ileum and colon in 48%, in terminal ileum only in 5%, in colon only in 52%. Granuloma was found in 40.3% of CD patients. In UC, disease located in the upper GI tract was seen in 32.1%, pancolitis 71%, left-sided colitis in 11%, proctitis in 15%. In children below 8 yrs, predominance of pancolitis was greater than in older children.
Conclusions: This prospective study presents unique data on a large European cohort of children with newly diagnosed IBD. The pediatric phenotype of both CD and UC is significantly different from adults. Further collaborative studies based on this ongoing European data collection will provide essential information on disease behavior, treatment and outcome of early onset IBD.

Can three-dimensional endoanal ultrasonography detect external anal sphincter atrophy? A comparison with endoanal magnetic resonance imaging

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Anal sphincter atrophy is associated with a poor clinical outcome of sphincter repair in patients with faecal incontinence. Preoperative assessment of sphincter is therefore relevant. External anal sphincter (EAS) atrophy can be detected by endoanal magnetic resonance imaging (MRI), but not by conventional endoanal ultrasonography (EUS). Three-dimensional EUS allows multiplanar imaging of the anal sphincters and thus enables more reliable anal sphincter measurements. The aim of the present study was to establish whether 3D EUS measurements can be used to detect EAS atrophy. For this purpose 3D EUS measurements were compared to endoanal MRI measurements.Patients with symptoms of faecal incontinence underwent 3D EUS and endoanal MRI. Internal anal sphincter (IAS) and EAS defects were assessed on 3D EUS and endoanal MRI. EAS atrophy was determined on endoanal MRI. The following measurements were performed: EAS length, thickness and area. Furthermore, EAS volume was determined on 3D EUS and compared to EAS thickness and area measured on endoanal MRI.Eighteen parous females (median age 56 years, range 32-80) with symptoms of faecal incontinence were included. IAS defects were seen in 7 (38%) patients on 3D EUS and in 8 (44%) on endoanal MRI. For EAS defects this was 14 (77%) on 3D EUS and 16 (88%) on endoanal MRI. Agreement between 3D EUS and endoanal MRI was 61% for IAS defects and defects 88% for EAS. EAS atrophy was seen in all patients on endoanal MRI. Correlation between the two methods for EAS thickness (r=0.003), length (r=0.05) and area (r=0.26) was poor. In addition, correlation was also poor for EAS volume determined on 3D EUS and EAS thickness (r=-0.08) and area (r=-0.77) measured on endoanal MRI.Conclusions: Three-dimensional EUS can be used for detecting EAS defects but no 3D EUS measurements are suitable parameters for assessing EAS atrophy.

Immune stimulating effects of β-glucan on enterocytes in vitro: a possible role for dectin-1

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β-glucans are fibers present in the cell wall of yeast, fungi but also in cereals like oat and barley. Immune stimulating effect of β-glucans extracted from yeast and fungi on macrophages have been reported. These effects are mediated by the β-glucan receptor dectin-1. Despite some differences in structure as compared to yeast and fungal glucans, also oat β-glucan has immune stimulating effects on macrophages. In addition, intragastric injection of oat β-glucan in C57BL/6 mice enhanced resistance to bacterial challenge. Since it is unlikely that oat β-glucan is taken up from the lumen into the circulation, we suggest an effect of oat β-glucan in the intestine. At first we questioned if enterocytes would respond to oat β-glucan and if so whether this effect could be explained by the presence of dectin-1. Ileostomic contents from 6 subjects who had consumed in random order a diet with or without oat β-glucan (5 g) were freeze-dried and pooled for 24 hour. Fecal water was prepared and a concentration of 6.5 mg/mL, containing 120-180 μg/mL oat β-glucan or no β-glucan (placebo), was added to four different intestinal cell lines (HT-29, T84, INT407 and differentiated Caco-2), which were stimulated with a cytokine mixture of interferon (IFN)-γ (100 U/mL), interleukin (IL)-1β (50 U/mL), and tumor necrosis factor (TNF)-α (10 ng/mL). After 16 hours interleukin (IL)-8 production was measured by ELISA, intracellular adhesion molecule (ICAM)-1 expression was determined by FACS analysis, and inflammatory protein expression profiles were determined with an antibody array. Finally, in INT407 cells, dectin-1 mRNA was detected by RT-PCR, and in addition effects of adding glucan phosphate (50, 100 and 200 μg/mL) to placebo fecal water on IL-8 production was determined. Overall, β-glucan enriched fecal water increased the inflammatory status of enterocytes as compared to placebo in all four cell lines. The addition of 50, 100 and 200 μg/mL glucan phosphate to placebo fecal water increased IL-8 production in INT407 cells by 16%, 21% and 49% respectively. This suggests that the effects of β-glucan enriched fecal water were indeed due to β-glucans. Since we also detected dectin-1 mRNA in INT407 cells, we conclude that the immune stimulating effects of dietary oat β-glucan on enterocytes were very likely mediated by dectin-1. However, this assumption needs further confirmation.

Glucocorticoids inhibit T cell receptor signaling via Lck and Fyn; a new immunosuppressive mechanism for an old drug

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Glucocorticoids (GCs) form the basis of current IBD treatment and induce immunosuppressive effects via GC receptor-dependent genomic effects. There is increasing evidence for rapid nongenomic GC effects, which can not be explained by the traditional mode of GC action. The aim of this study was to define nongenomic GC effects. CD4+ T lymphocytes were pretreated for 10 minutes with the synthetic GC analogue dexamethasone and activated with anti-CD3 and anti-CD28 Abs for 15 minutes. Cell lysates were used for peptide arrays containing 1176 different kinase consensus substrates and the results were validated with conventional techniques. Peptide array analysis revealed marked early differences in phosphorylation patterns between GC-treated and non-GC-treated cells. GC-induced suppressed phosphorylation of Lck/Fyn kinase substrates was observed, indicating reduced enzymatic activities of Lck and Fyn, key players in T cell receptor (TCR) signaling. Subsequent immunoprecipitation experiments demonstrated GC-induced inhibition of Lck and Fyn recruitment to the TCR complex, a crucial step for Lck/Fyn-mediated TCR signaling. Western blot analysis showed impaired phosphorylation of a series of downstream Lck/Fyn targets, including PKB, PKC, ERK, JNK and p38 MAPKs due to short-term GC treatment. In vitro kinase assays using RU486 as a GC receptor ligand revealed a GC receptor-dependent mechanism of reduced Lck/Fyn activities. Finally, parallel experiments conducted following the application of GCs in healthy individuals confirmed suppression of Lck and Fyn in T cells within 1 hr in vivo. This study identifies a nongenomic immunosuppressive effect of GCs based on impaired Lck/Fyn-mediated TCR signaling. We hypothesize that agents selectively targeting Lck and/or Fyn could constitute a novel potent immunosuppressive therapy.

Villous atrophy in celiac disease: uncovering the patho-mechanisms by immunohistochemistry and gene-expression studies

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Coeliac disease (CD) is an inflammatory disorder of the small intestine characterized by a permanent intolerance to gluten-derived peptides. When those peptides reach the lamina propria, they provoke changes, villous atrophy. A key question in CD is what mechanism(s) cause villous atrophy. The following four mechanisms might drive such changes, apoptosis, oxidative stress, matrix metalloproteinases and/or disturbed proliferation/differentiation. In this study we investigated the involvement of the proposed mechanisms by immunohistochemistry and microarray gene expression studies. Both microarray hybridizations (MA) and immunohistochemistry were performed with duodenal biopsies from CD patients in various stages of recovery on a gluten-free diet (Marsh III – Marsh 0). For each mechanism one or more antigens were selected, detected by polyclonal or monoclonal antibodies. Disturbed proliferation/differentiation pathways were shown both with IH and MA. The most striking difference was observed with a TransMembrane 4 SuperFamily 4 (TM4SF4) gene involved in the regulation of differentiation of enterocytes. A gradual decrease in TM4SF4 expression (M0-MIII) was observed on the apical site of epithelial cells. This was confirmed by qRT-PCR (nine-fold reduced). Other differentiation markers like alkaline phosphatase (AP) and fatty acid binding protein 1 (FABP1) were also reduced. Proliferation marker ki-67 was increased in patients. Metalloproteinase (MMP3) was differentially expressed (2-fold up) in MA but not in IH. The genes iNOS and caspase 3, markers for oxidative stress and apoptosis, respectively were not differentially expressed in MA. However, in IH, iNOS did show a slight increase in CD patients compared to controls. Caspase 3 in IH was uniformly expressed in both patients and controls. Our results do not suggest that either apoptosis, metalloproteinases or oxidative stress are likely to provoke villous atrophy. However, disturbed proliferation/differentiation pathways do seem to be involved. Differentiation markers like TM4SF4, AP and FABP1 were reduced in patients while the proliferation marker ki-67 was increased. Differential expression correlated with the degree of mucosal restructuring. Conceivably, a reduction of TM4SF4 expression marks the abrogated terminal differentiation of enterocytes.These results may change our perception of the patho-mechanisms of CD with possible implications for diagnostics and therapy.

The systemic cytokine response during experimental acute pancreatitis: impact of enteral probiotics

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In the course of severe acute pancreatitis, mortality usually occurs early or late. Early mortality is often associated with severe systemic inflammatory response syndrome (SIRS), whereas late mortality can be attributed to secondary infection of pancreatic necrosis. In both phases, the intestinal flora plays an important regulatory role. Selected probiotics are able to modulate intestinal flora. Aims of this study were: 1) to correlate early and late phase plasma levels of various cytokines and chemokines to clinical outcome, and 2) assess the effect of probiotics on immune responses.
Acute pancreatitis was induced in male Sprague-Dawley rats by intraductal bile salt infusion (glycodeoxycholate, 15 mM) followed by pancreatic hyperstimulation (intravenous cerulein, 5 µg/kg/hr, for 6 hours). Probiotics or placebo were administered daily via a permanent gastric cannula, from five days prior to until seven days after induction of pancreatitis. Plasma cytokine levels were determined before, and 6 hrs, 24 hrs and 7 days after induction of pancreatitis. The presence of bacteraemia was assessed by cultivation of blood, sampled 7 days after induction of pancreatitis.
In the course of severe acute pancreatitis, specific 'cytokine signatures' were identified to be predictive for outcome: 1) elevated IL-6, IL-10 and CXCL1 levels were associated with early mortality, 2) increased TNF-α and IL-1β predict bacteraemia potentially causing late mortality, 3) an early and self-resolving IL-10 response was found in animals protected from early mortality, whereas sustained IL-10 levels were associated with bacteraemia.
Probiotic treatment reduced late phase mortality and bacteraemia with gram-negative or anaerobic bacteria. Effects of probiotics on cytokine responses to acute pancreatitis were: 1) significantly reduced CXCL1 levels, preventing unfavourable neutrophil activation and associated remote organ damage, 2) reduced variation of key pro-inflammatory cytokines, preventing hyper- and hyporesponsiveness of the immune system to acute pancreatitis.
Conclusions: Specific pro-inflammatory and regulatory cytokine combinations are predictive for mortality and bacteraemia during severe acute pancreatitis. Probiotics prevent unfavourable hyper- or hyporesponsive immune reactions and improve outcome.
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C-reactive protein and natural IgM antibodies are activators of complement in a rat model of intestinal ischemia and reperfusion

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The involvement of C-Reactive Protein (CRP), immunoglobulin M (IgM), and natural IgM to phosphorylcholine (anti-Pc IgM) in complement activation, was investigated in a rat model of intestinal ischemia and reperfusion (II/R) by administration of C1-esterase inhibitor (C1-Inh) either prior to or after ischemia. Rats were subjected to 60 min of superior mesenteric artery occlusion and 3 hours of reperfusion. Intravenous administration of vehicle (human albumin) or C1-Inh (200 U/kg) was performed before (n=8) or after ischemia (n=8). Sham animals did not undergo ischemia (n=6/group). II/R significantly increased levels of C4b/c, CRP, IgM, anti-Pc IgM in intestinal homogenates. A strong correlation was observed between C4b/c-CRP levels in the homogenates (Rs 0.769, $p<0.01$). Between CRP-IgM and CRP-anti Pc IgM a correlation of 0.529 ($p<0.05$) and 0.511 ($p=0.051$) respectively, was observed. The correlation between C4b/c-IgM was 0.406 ($p=0.133$).Furthermore, clear depositions of C3, CRP and IgM in intestinal tissue were demonstrated after II/R. C1-Inh prior to ischemia reduced the complement activation response following II/R, as reflected by decreased levels of C4b/c in conjunction with reduced anti-Pc IgM, in the intestinal homogenates. C1-inh post-ischemia also reduced C4b/c levels in the homogenates and attenuated the neutrophil influx. C1-inh administration post ischemia resulted in a non-significant decrease of C3 depositions and intestinal injury. C1-Inh also diminished the leakage of albumin when administrated prior to ischemia. These data suggest that complement activation induced by natural antibodies and/or CRP is attenuated by C1-Inh. Administration of C1-Inh in mesenteric ischemia may be beneficial to prevent or reduce intestinal ischemia and reperfusion injury via a reduction of complement activation, leading to a reduced inflammatory response.

Comparison of kinase profiles in Barrett's esophagus, normal squamous esophagus and normal gastric cardia proves that Barrett's esophagus has a high glycolytic activity.

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Background: Barrett's esophagus (BE) is the metaplastic process in which the normal squamous epithelium of the distal esophagus is replaced by columnar lined epithelium. To gain more insight into the molecular and cellular mechanisms in the development of BE, the aim of this study was to create a comprehensive description of cellular kinase activity occurring in BE, normal squamous esophagus and gastric cardia.
Material and Methods: To produce a global analysis of cellular kinase activity present in these tissues, peptide arrays exhibiting 1176 specific consensus sequences for protein kinases were used. We compared the cellular kinase activities between BE and its surrounded epithelium. Interesting differences in kinase activity were validated by conventional technology in tissue samples of 27 BE patients.
Results: Three unique kinome profiles were compared. Results, validated by Western blot analysis, showed that in BE the Mitogen-Activated Protein kinase signaling cassette is decreased probably partly due to increased inhibition of c-Raf through Rab. One of the most prominent differences between Barrett's metaplasia and normal squamous epithetlium was the significant decreased phosphorylation of Src consensus substrates. Furthermore we found that EGF receptor activity is decreased in BE compared to normal squamous epithelium, but its activity is increased compared to gastric cardia. In addition kinome analysis demonstrated that glycolysis is an important process in BE. Validation of pyruvate kinase activity showed that its activity is significantly up-regulated in BE compared to normal squamous and gastric cardia epithelium. Earlier we have found with cluster and gene expression profile analysis on BE, normal squamous and gastric cardia mucosa that metabolism was one of the most important biological processes in BE. Further investigation in this metabolism group revealed that glycolysis was the most prominent process in this cluster.
Conclusions: Using an array of pseudo kinase-substrates we demonstrated that BE has strong similarities with both the kinome profiles of normal squamous and normal cardia epithelia. This study contributes to a better understanding of kinase activities, and several signal transduction pathways and cellular functions that are associated with BE. Future manipulations of these pathways will help us to treat BE and prevent the development of the associated esophageal adenocarcinoma.

Regulation and role of the two Helicobacter mustelae TonB orthologs in iron acquisition

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Helicobacter mustelae is a gastric pathogen of ferrets. Like almost all bacterial pathogens, Helicobacter species require iron for growth. However, iron-sequestration by mucosal surfaces is a non-specific defense host mechanism against bacterial pathogens, and conversely iron acquisition is considered an important bacterial virulence factor. Iron-transport in Gram-negative pathogens is energized via the TonB-ExbB-ExbD complex. The H. mustelae genome sequence contains two genes encoding TonB orthologs, a situation similar to that of H. pylori. In this study we have characterized the regulation and function of the two TonB orthologs of H. mustelae. Isogenic tonB mutants were created in H. mustelae strain ATCC 43772 by insertional mutagenesis. The wild-type strain and tonB mutants were plated under iron-limited conditions, and hemin, hemoglobin or ferric citrate were supplemented as sole iron source. The growth promotion zone was measured after 48h incubation. Regulation of tonB1 and tonB2 expression was assessed by Northern hybridization. Homology searches of the preliminary release of the H. mustelae genome sequence allowed the identification of two TonB orthologs, tentatively named tonB1 and tonB2. Wild-type H. mustelae was able to utilize iron chloride, ferric citrate, hemoglobin and hemin as sole iron source. A tonB1 mutant was unable to grow with hemin as sole iron source, but was not affected in growth on the other tested iron sources. In contrast, mutation of the tonB2 gene resulted in reduced growth with ferric citrate and hemoglobin as sole iron source. Transcription of tonB1 was iron- and nickel-repressed, whereas transcription of tonB2 was not affected by changes in iron or nickel availability. Conclusions: The two TonB orthologs of H. mustelae have differential roles in iron acquisition, with TonB1 functioning in hemin uptake. Interestingly, hemin and hemoglobin uptake seem to require different TonB orthologs, suggesting that different receptors are involved in this process. The TonB orthologs of H. mustelae are differentially regulated, which allows for additional finetuning of iron uptake. This adds another dimension to the intricate process of adaptation of Helicobacter species to the conditions occuring in the gastric mucosa.

Impaired immune recognition of M. tuberculosis and M. paratuberculosis in Crohn patients homozygous for the NOD2 3020insC mutation

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Mutations in de NOD2 gene are associated with Crohn's disease. NOD2 is an intracellular pathogen recognition receptor (PRR) which recognizes bacterial peptidoglycans and activates the innate immune response. This implies that a disturbed recognition of intracellular pathogens leads to an impaired host defense and might play a role in the pathogenesis of Crohn's disease (CD). Therefore, we investigated the role of NOD2 in the innate immune response against M. tuberculosis and M. paratuberculosis. PBMC's and macrophages of healthy volunteers (HV), CD patients without 3020insC (NOD2wt) mutation, heterozygous (NOD2het) or homozygous for the 3020insC mutation (NOD2fs), were stimulated with M. tuberculosis and M. paratuberculosis killed by sonication. Cytokine response was measured (IL-1beta, TNFalfa en IL-10) after 24 hours by ELISA.PBMC's (n=5 in each group) stimulated with M. tuberculosis produced significant less IL-1beta in NOD2fs (698±256 pg/ml) compared with HV (2600±499 pg/ml), NOD2wt (2743±464 pg/ml) and NOD2het (2284±386 pg/ml), $p<0.05$. A significant difference was also found between NOD2fs and the other three groups in the production of TNFalfa (2-fold decrease, $p<0.05$) and IL-10 (5-fold decrease, $p<0.05$). When stimulated with Pam3Cys (TLR2 ligand) there was no difference in cytokine production between HV, NOD2wt, NODhet and NOD2fs. Macrophages (n=2 in each group) stimulated with M. tuberculosis produced less TNFalfa in NOD2fs than HV (1019 ±252 vs 4390±2164 pg/ml). Macrophages from NOD2fs patients also produced less TNF when stimulated with M. paratuberculosis (428±228 vs 3346±607 pg/ml). No difference was measured after stimulation with Pam3Cys.
Conlusion: PBMC's and macrophages of homozygous 3020insC Crohn patients stimulated with M.tuberculosis and M. paratuberculosis produce in vitro less cytokines compared to healthy volunteers, CD patients without or CD patients heterozygous for the 3020insC mutation. The role of NOD2 for the recognition of M. paratuberculosis may provide an additional argument that this microorganism is involved in the pathogenesis of Crohn's disease.

Bone Morphogenetic Protein (BMP) signaling regulates fundic gland homeostasis and suppresses tumorigenesis at gastric epithelial transition zones in mice

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Epithelial cells at the junction of two distinctive epithelial tissues are prone to receive conflicting information from the two different epithelial environments. This may make cells at epithelial junctions more vulnerable to tumorigenesis. Two important clinical examples of tumors associated with epithelial transition zones in humans are carcinomas that arise at the squamocolumnar junctions of the esophagogastric transition zone and the uterine cervix. Morphogens regulate epithelial homeostasis in the gastrointestinal tract. Bone Morphogenetic Protein (BMP) signaling stimulates apoptosis and suppresses tumorigenesis in the small and large intestine. Here we examine the role of BMP signaling in the murine stomach. We examined the expression of the BMP signaling receptors Bmpr1a and Bmpr1b and the localization of the phosphorylated (active) form of Smad1. We studied the role of the Bmpr1a in conditional Bmpr1a knock-out mouse.The BMP signaling receptors are differentially expressed in the gastric epithelium. Bmpr1a is expressed in the gastric glands and by epithelial cells at the esophagogastric and gastrointestinal transition zones. Bmpr1b is expressed by gastric pit (foveolar) cells and mesenchymal cells. Upon conditional inactivation of Bmpr1a mice develop fundic gland hyperplasia. Interestingly, these mice develop polyps that may develop intraepithelial neoplasia (dysplasia) specifically in the esophagogastric and gastrointestinal transition zones. We show that these transition zones are distinct areas of epithelium that lack some of the signals for differentiation of the adjacent gastric epithelium and show increased proliferation. Conclusions: Here we show that BMP signaling through Bmpr1a not only regulates fundic gland homeostasis but also specifically suppresses tumorigenesis at gastric epithelial transition zones in the mouse. This is the first example of a pathway that controls homeostasis at the junction between different epithelial layers. Our data may have important implications for the understanding of the genesis of esophagogastric tumors in humans.

Alfabetische lijst van standhouders voorjaarscongres 2006 - **B = Beneluxhal K = Kempenhal M = Meierij foyer**

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