Programma voorjaarsvergadering 20 en 21 maart 2003

NEDERLANDSE VERENIGING VOOR GASTROENTEROLOGIE

Sectie Gastrointestinale Endoscopie

Netherlands Society for Parenteral and Enteral Nutrition

Sectie Endoscopie Verpleegkundigen en Assistenten

Sectie Maagdarmmotoriek

Sectie Experimentele Gastroenterologie

Sectie Kindergastroenterologie

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NEDERLANDSE VERENIGING VOOR HEPATOLOGIE

★

NEDERLANDSE VERENIGING VOOR GASTROINTESTINALE CHIRURGIE

★

NEDERLANDS GENOOTSCHAP VAN MAAG-DARM-LEVERARTSEN

★

NH KONINGSHOF

VELDHOVEN

INHOUDSOPGAVE **pagina**

VOORWOORD

Hierbij treft u het volledige programma aan van de komende voorjaarsvergadering te Veldhoven, inclusief de abstracts.

Naast vrije voordrachten door de verschillende secties en verenigingen, wordt op donderdagmiddag een minisymposium verzorgd door de Nederlandse Vereniging voor Gastrointestinale Chirurgie, getiteld 'Chirurgische en medicamenteuze mogelijkheden bij motitiliteitsstoornissen van de tractus digestivus'. In de Baroniezaal vindt voorts de presentatie van de CBO richtlijn Maagklachten plaats, deze bijeenkomst start om 15.30 uur.

Donderdagmiddag wordt om 17.00 uur in de Brabantzaal de eerste 'Guido Tytgat-Lecture' gehouden. Deze lezing - gesponsord door Tramedico/Falk - wordt verzorgd door Dr. D. Pessayre. Alle leden worden van harte uitgenodigd hierbij aanwezig te zijn!
Donderdagavond is er een plenaire sessie met de traditionele state of the art lecture, gehouden door Prof. Alan Cameron uit de VS, dit in het kader van de ALTANA -lecture.

Vrijdagochtend verzorgt de Sectie Gastrointestinale Endoscopie in de Brabantzaal een programma 'De scoop op de richtlijn bloedingen'. Daarnaast is er vrijdag de hele dag een symposium georganiseerd door de Nederlandse Vereniging voor Hepatologie en de Werkgroep Klinische Virologie, getiteld**: '**Dutch Symposium on Chronic Hepatitis B and C: Virology and Therapeutic Options'. De Vereniging voor Maag-Darm-Leververpleegkundigen en de Sectie Endoscopie Verpleegkundigen en Assistenten hebben op respectievelijk vrijdagochtend en vrijdagmiddag een eigen programma. Daarnaast verschillende sessies met vrije voordrachten in de Brabantzaal, de Baroniezaal en Zaal 80.

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

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

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

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

Programma donderdag 20 maart 2003

DONDERDAG	BRABANTZAAL	BARONIEZAAL	PARKZAAL	ZAAL 80	AUDITORIUM
14.00-15.30	Vrije voordrachten Nederlandse Vereniging voor Gastrointestinale Chirurgie p. 7	Vrije voordrachten Netherlands Society of Parenteral and Enteral Nutrition p. 8-9	Vrije voordrachten Netherlandse Vereniging voor Gastroenterologie p. 11-13	Geen programma in deze zaal op donderdag	Vrije voordrachten en Nederlandse Verenging voor Hepatologie p. 13-15
15.30-16.00	Theepauze	Aanvang CBO-richtlijn 15.30 uur!	Thee		Theepauze en ledenvergadering
16.00-17.00	Mini-symposium: Chirurgische en medi-camenteuze mogelijk-heden bij motitiliteits-stoornissen van de tractus digestivus - p. 8	Concept-advies CBO-richtlijn Maagklachten p. 10	Vrije voordrachten Netherlandse Vereniging voor Gastroenterologie p. 11-13		Vrije voordrachten en Nederlandse Verenging voor Hepatologie p. 13-15
17.00	'Guido Tytgat lecture' door Dr. D. Pessayre p.16				
17.30	Congresborrel en diner				
20.00	Vrije voordrachten NVGE p. 16				
21.00	ALTANA-lecture - p. 16 Prof. A. Cameron, U.S.A.				
21.30	Ledenvergadering NVGE				
22.00	Borrel in “Dommelpoort” aangeboden door AstraZeneca				

Programma vrijdag 21 maart 2003

VRIJDAG	BRABANTZAAL	BARONIEZAAL	PARKZAAL	ZAAL 80	AUDITORIUM
09.00	Casuïstiek voor de klinikus p. 17	Vrij voordrachten Nederlandse Vereniging voor Gastroenterologie p. 18-19		Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie p. 20-21	Dutch symposium on chronic hepatitis B and C: virology and therapeutic options p. 23-24
10.00	De scoop op de richtlijn bloedingen p. 17 Vrije voordrachten p. 17	Vrije voordrachten Sectie Experimentele Gastro-enterologie p. 19-20	Programma Vereniging van Maag-Darm-Lever Verpleegkundigen p. 22	Vervolg vrije voordrachten NVGE p. 20-21	Vervolg symposium p. 23-24
11.00	Koffiepauze	Koffiepauze	Koffiepauze	Koffiepauze	Koffiepauze (10.30)
11.30	Vrije voordrachten Sectie Gastrointestinale Endo-scopie p. 17	International teaching session 'Apoptosis in Hepato-Gastro-enterology' p. 20	Programma Vereniging van Maag-Darm-Lever Verpleegkundigen p. 22	Vervolg vrije voordrachten NVGE p. 20-21	Vervolg symposium p. 23-24
12.30	Lunch	Lunch	Lunch	Lunch	Lunch
14.00	Programma Sectie Endoscopie Assistenten p. 29	Vrije voordrachten Sectie Experimentele Gastro-enterologie p. 25-27		Vrije voordrachten Sectie Maagdarmmotoriek p. 27-28	Dutch symposium on chronic hepatitis B and C: virology and therapeutic options (aanvang 13.30!) p. 24
16.00	Theepauze/einde programma	Theepauze/einde programma		Theepauze/einde programma	Theepauze/einde programma

CURSORISCH ONDERWIJS IN MAAG-DARM-LEVERZIEKTEN **AUDITORIUM**
19 - 20 MAART 2003

Cursuscommissie:	Dr. W.A. Bemelman (chirurg AMC) B. van Wijnhoven (AGIO Heelkunde, Delft) Dr. H.M. van Dullemen (maag-darm-leverarts AZG) Dr. P. Honkoop (maag-darm-leverarts i.o., Erasmus MC) Dr. C.M.F. Kneepkens (kinderarts, VUMC) Prof. dr. C.J.J. Mulder (voorzitter) (maag-darm-leverarts, VUMC)

Woensdag 19 maart 2003

20.30 - 21.00 uur	IBD Etiologie en epidemiologie in Nederland *Dr. M.G.V.M. Russel, Medisch Spectrum Twente*
21.00 - 21.30 uur	Collagene colitis Een separate entiteit? *Prof. Dr. C.J.J. Mulder*
21.30 - 22.00 uur	5-ASA: topicaal/oraal: bij wie nog? *Dr. R.A. van Hogezand, LUMC*
22.00 - 22.30 uur	Iedereen met IBD: Azathioprine *Dr. H.M. van Dullemen, AZG*

Donderdag 20 maart 2003

08.30 - 08.55 uur	Methotrexaat en Ciclosporine?, doen wij het nog? *Dr. D.W. Hommes, AMC*
08.55 - 09.20 uur	6TG een aanwinst?, vervangt Azathioprine? *Dr. D. de Jong, UC St. Radboud*
09.20 - 09.50 uur	Cytokine-modulatie: de enige weg? Geven we genoeg Infliximab? *Dr. D.W. Hommes, AMC / Prof. dr. S.J.H. v. Deventer, AMC*
09.50 - 10.15 uur	Gaan we te lang conservatief door? *Dr. J.F.M. Slors, AMC*

KOFFIE

10.45 - 11.20 uur	Chirurgie bij IBD *Dr. C.J.H.M. v. Laarhoven, St. Elisabeth Ziekenhuis, Tilburg*
11.20 - 11.40 uur	Probiotica / Antibiotica bij pouchitis *Dr. W.R. Schouten, Erasmus MC*
11.40 - 12.30 uur	Pouchsurvival/complications *Prof. Dr. R.J. Nicholls,* *St. Marks Hospital, Harrow (London)*

LUNCH

Nederlandse Vereniging voor Gastrointestinale Chirurgie **Brabantzaal**

13.30 Inschrijving, koffie

Voorzitters: O.R.C. Busch / E.H. Eddes

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

14.00 Revision of previously undefined gastrointestinal mesenchymal tumors results in a high rate of actual stromal (GIST) tumors (p. 30)
H.J.P. de Schipper, R.S.L. Liem, H.F.G.M. van den Ingh, E. van der Harst. MCRZ, Locatie Clara, Rotterdam.

14.10 Surgical management of ampullary tumours: local or extensive resection (p. 31)
S.M.M. de Castro, N.T. van Heek, O.R.C. Busch, T.M. van Gulik, H. Obertop, D.J. Gouma. Dept of Surgery, Academic Medical Centre Amsterdam, The Netherlands

14.20 Prospective randomized controlled multi-center trial evaluating prophylactic gastrojejunostomy for unresectable pancreatic head cancer - interim analysis - (p. 32)
N.T. van Heek[1], S.M.M. de Castro[1], R.C.I van Geenen[1], E.J. Hesselink[2], T.C.K. Tran[3], G. Kazemier[3], P.J. Breslau[4], O.R.C. Busch[1], H. Obertop[1], D.J. Gouma[1]. Dept of Surgery, Academic Medical Center Amsterdam[1], Amsterdam, Hospital Gelre Apeldoorn[2], Apeldoorn, University Hospital Dijkzigt[3], Rotterdam, Hospital Rode Kruis[4], The Hague, The Netherlands

14.30 Hospitalization (readmission) after surgical treatment of patients with pancreatic adenocarcinoma (p. 33).
K.F.D. Kuhlmann, S.M.M. de Castro, O.R.C. Busch, T.M. van Gulik, H. Obertop, D.J. Gouma. Dept of Surgery, Academic Medical Center, Amsterdam, The Netherlands

14.40 Ex vivo sentinel node procedure in patients with colorectal carcinoma; a feasible technique (p. 34).
A.A.W. van Geloven[1], E.G.J.M. Pierik[1], F.C.P. Moll[2], J.E. Boers[2]. Dept of Surgery[1], and Pathology[2], Isala Klinieken (loc. Weezenlanden), Zwolle, The Netherlands

14.50 Disturbances in fecal continence after Transanal Endoscopic Microsurgery (TEM).
(p. 35). L.P.S. Stassen, T. Karsten. Dept of Surgery, Reinier de Graaf Groep, Delft/Voorburg, The Netherlands

15.00 Sacral nerve stimulation for fecal incontinence (p. 36)
S. Koch, Ö. Uludag, W. van Gemert, C. Baeten, Academic Hospital Maastricht, The Netherlands.

15.10 Health status and quality of life after Ileo Neo Rectal Anastomosis (INRA) in comparison to Ileo Pouch Anal Anastomosis (IPAA) (p. 37).
W. Hueting[1], J. de Vries[2], C.J.H.M. van Laarhoven[3], H.G. Gooszen[1]. Dept of Surgery[1], University Medical Centre Utrecht, Utrecht, Dept of Psychology[2], Tilburg University, Dept of Surgery[3], St. Elisabeth Hospital, Tilburg, The Netherlands.

15.20 Does experience influence outcome of laparoscopic Nissen fundoplication? (p. 38)
R.K.J. Simmermacher[1], H.J.M. Oostvogel[2], P.J.J. van Rijn[3], M.A. Cuesta-Valentin[4], J.J.B van Lanschot[5], L.P. Stassen[6], H.G. Gooszen[1]. Dept of Surgery[1], University Medical Center, Utrecht, Dept of Surgery[2], St. Elisabeth Hospital, Tilburg, Dept of Surgery[3], 't Lange Land Hospital, Zoetermeer, Dept of Surgery[4], VU Medical Center, Amsterdam, Dept of Surgery[5], Academic Medical Center, Amsterdam, Dept of Surgery[6], Reinier de Graaf Gasthuis, Delft, The Netherlands.

15.30 Theepauze

16.00 **MINISYMPOSIUM**
Chirurgische en medicamenteuze mogelijkheden bij motiliteitsstoornissen van de tractus digestivus

Voorzitters: W.A. Bemelman / C.J.H.M. van Laarhoven

Achalasie
G.E.E. Boeckxstaens, maag-darm-leverarts
Academisch Medisch Centrum, Amsterdam

Gastroparese
J. Tack, maag-darm-leverarts
Katholieke Universiteit Leuven, België

Slow transit obstipatie
R.M.H.G. Mollen, chirurg
Ziekenhuis Gelderse Vallei, Ede

17.00 **Voor de 'Guido Tytgat lecture' kunt u zich begeven naar de Brabantzaal**
'Mechanisms of liver injury in steatohepatitis'.
Dr. D. Pessayre, Hôpital Beaujon, Clichy, France.

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

13.30 Ontvangst, inschrijving, koffie

Voorzitters: N.E.P. Deutz / J.B. van Goudoever

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

14.00 The role of NOS-2 and NOS-3 in renal and muscle protein metabolism during early endotoxemia in mice (p. 39 + p. 40)
Y.C. Luiking[1], M.M. Hallemeesch[1], W.H. Lamers[2], P.B. Soeters[1], N.E.P. Deutz[1]. Depts of Surgery[1] and Anatomy[2], Maastricht University, The Netherlands.

14.10 Low plasma arginine concentrations in tumour-bearing mice are not compensated by increased de novo arginine production in the kidney (p. 41).
Y.L.J. Vissers, Y.C. Luiking, C.H.C. Dejong, M.F. von Meyenfeldt, N.E.P. Deutz. Dept of Surgery, Maastricht University, The Netherlands

14.20 Mannan-binding Lectin Plasma Levels in the Acute Phase Response Following Major Abdominal Surgery: a 'Not So Acute' Phase Protein (p. 42)
J.W.O. van Till[1] , M.A. Boermeester[1], J.W. van Sandick[1], M. Hart[2], B. Lamme[1], J.J.B. van Lanschot[1], L.A. Aarden[2]. Dept of Surgery[1], Academic Medical Center, Amsterdam Central Laboratory of The Netherlands Red Cross Blood Transfusion Service (CLB)[2], Dept of Immunopathology, Amsterdam.

14.30 Gene expression in the human small intestine. Mediating effects of iron-induced lipid peroxidation (p. 43)
F.J. Troost[1], W.H.M. Saris[1], R-J.M. Brummer[2]. Dept of Human Biology[1], NUTRIM, Maastricht University, Maastricht and Dept of Gastroenterology[2], NUTRIM, University Hospital Maastricht, Maastricht, The Netherlands.

14.40 Normal 24 hours pattern of gastric and jejunal PCO2 in 10 healthy volunteers (p. 44)
P.B.F. Mensink, J.J. Kolkman, A.B. Huisman and R.H. Geelkerken. Dept of Gastro-enterology, Radiology and Vascular Surgery, Medisch Spectrum Twente, Enschede.

14.50 First results of 24 hours gastric and jejunal PCO2 measurement in the diagnosis of chronic mesenteric ischemia (p. 45)
P.B.F. Mensink, J.J. Kolkman, A.B. Huisman and R.H. Geelkerken. Dept of Gastro-enterology, Radiology and Vascular Surgery, Medisch Spectrum Twente, Enschede.

15.00 The lactose digestive capacity in children with small intestinal mucosal damage: Relation between the new ^{13}C/2H-glucose test and the lactase activity measured in SBB specimens* (p. 46)
H.A. Koetse[1], G. Gonera-de Jong[1], M. Priebe[2], F. Stellaard[2], R.J. Vonk[2]. Beatrix Childrens Hospital[1], Laboratory of Nutrition and Metabolism[2], University Hospital Groningen, Groningen, The Netherlands.

15.10 Hydrogen breath tests and abdominal symptoms: how well do they correlate? (p. 47)
P.P.J. van der Veek, A.A.M. Masclee. Dept of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands.

15.20 Survival of the probiotic L. plantarum 299V in the gastrointestinal tract with and without gastric acid inhibition (p. 48)
D. Goossens[1], D. Jonkers[1], M. Russel[1], E. Stobberingh[2], A. van den Bogaard[2], R. Stockbrügger[1]. Dept of Gastroenterology[1] and Medical Microbiology[2], University Hospital Maastricht, Netherlands.

15.30 Einde programma NESPEN

donderdag 20 maart 2003

Conceptadvies CBO richtlijn maagklachten **Baroniezaal**

Voorzitter: R.W.M. van der Hulst

15.30 Inleiding door de voorzitter
R.W.M. van der Hulst

Achtergrond en historie van de werkgroep
N. de Wit, huisarts, voorzitter CBO werkgroep

Presentatie stroomdiagram
N. de Wit, huisarts, voorzitter CBO werkgroep

Diagnostiek bij maagklachten
M. Numans, huisarts

Beleid bij persisterende maagklachten
N. de Wit, huisarts

H. pylori
W.A. de Boer

Farmacotherapie
H. Festen / E.C. Klinkenberg-Knol

Discussiepunten, stemming, standpuntbepaling
H. Festen

17.00 einde programma

17.00 **Voor de 'Guido Tytgat lecture' kunt u zich begeven naar de Brabantzaal**
'Mechanisms of liver injury in steatohepatitis'.
Dr. D. Pessayre, Hôpital Beaujon, Clichy, France.

17.30 Congresborrel / diner

Nederlandse Vereniging voor Gastroenterologie **Parkzaal**

13.30 Ontvangst, inschrijving, koffie

Voorzitters: E.C. Klinkenberg-Knol / J.W. Greve

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

14.00 Adenocarcinomas of the gastric cardia versus the esophagus: a comparative study with respect to cyclooxygenase-2 expression. (p. 49)
C.J. Buskens[1], A. Sivula[2], M. Westerterp[1], G.J.A. Offerhaus[3], A. Ristimäki[2], J.J.B. van Lanschot[1]. Depts of Surgery[1] , and Pathology[3], Academic Medical Center/ University of Amsterdam, Amsterdam, the Netherlands; and Dept of Pathology[2] , Molecular and Cancer Biology Research Program, Biomedicum Helsinki, University of Helsinki, Helsinki, Finland.

14.10 Is high dose rate brachytherapy an alternative to stent placement in the palliation of malignant dysphagia? - A randomized trial. (p. 50)
M.Y.V. Homs[1], E.W. Steyerberg[1], W.M.H. Eijkenboom[1], L.J.A. Stalpers[2], J.F.W.M. Bartelsman[2], H.K. Wijrdeman[3], C.J.J. Mulder[4], J.G. Reinders[5], H. Boot[6], B.M.P. Aleman[6], P.D. Siersema[1]. Erasmus MC / University Medical Center Rotterdam[1], Academic Medical Center[2], Amsterdam, University Medical Center Utrecht[3], Rijnstate Hospital[4], Arnhem, Arnhem Radiotherapeutic Institute[5], Antoni van Leeuwenhoek Hospital[6], Amsterdam; for the Dutch SIREC study group.

14.20 European multicentre study on celiac disease and non-Hodgkin lymphoma*
(p. 51-52))
M. Luisa Mearin[1] , C. Catassi[2], N. Brousse[3], R. Brand[4], P. Collin[5], E. Fabiani [2], J.J. Schweizer[1], Abuzakouk[6], H. Szajewska[7], C. Hallert[8], C. Farré Masip[9], G.K.T. Holmes[10] and other members of the Biomed Group. Depts of Pediatrics[1] and Medical Statistics[4] , Leiden University Medical Centre, The Netherlands; Dept of Pediatrics, University of Ancona[2], Italy; Necker-Enfants Malades Hospital School of Medicine[3], Paris, France; Depts of Internal Medicine and Oncology, Hospital and Medical School, Universtiy of Tampere[5], Finland; Dept of Immunology, St. James's Hospital, University of Dublin, Trinity College[6], Ireland; Dept of Pediatric Gastroentorology & Nutrition and Institute of Gastroenterology, Warsaw Medical School[7], Poland; Dept of Internal Medicine, Linköping Hospital[8], Sweden; Hospital Sant Joan de Déu, Esplugues (Barcelona)[9], Spain; Dept of Gastroenterology, Derbyshire Royal Infirmary[10], United Kingdom.

14.30 Hyperplastic polyps and hereditary nonpolyposis colorectal cancer (p. 53)
F.E.M. Rijcken[1], T. van der Sluis[2], H. Hollema[2], J.H. Kleibeuker[1]. Dept of Gastroenterology[1] and Pathology [2], University Hospital Groningen, The Netherlands.

14.40 Immunohistochemical expression (IHC) and microsatellite instability (MSI) analysis in families with clustering of colorectal cancer (p. 54)
A.E. de Jong[1], M. van Pijenbroek[2], C.M.J. Tops[3], J. Wijnen[3], P.F. Franken[3], A.H.J.T. Brocker-Vriends[3], H.F.A. Vasen[1,4], H.J. Morreau[2]. Dept of Gastroenterology[1] and Dept of Pathology[2] and Center for Human and Clinical Genetics[3], Leiden Medical University Center, The Netherlands, The Netherlands Foundation for the Detection of Hereditary Tumours[4].

donderdag 20 maart 2003

14.50 Tumor phenotype and genetic expression are not correlated with clinical behavior in rectal carcinoma after radiotherapy (p. 55)
I.D. Nagtegaal[1], C.G.S. Gaspar[2], C.A.M. Marijnen[3], C.J.H. van de Velde[4], R. Fodde[2], J.H.J.M. van Krieken[1]. Dept of Pathology[1], UMC St Radboud, Nijmegen, Depts of Clinical and Human Genetics[2], Clinical Oncology[3] and Surgery[4], LUMC, Leiden, The Netherlands.

15.00 In primary care IBS patients, concurrent anxiety and/or depression is associated with impaired Health Related Quality of Life (HRQoL) (p. 56)
A.H. Oberndorff-Klein Woolthuis[1], R-J.M. Brummer[1], J.W.M. Muris[2], N.J. de Wit[3], R.W. Stockbrügger[1]. Dept of Gastroenterology & Hepatology[1], University Hospital, Maastricht, Dept of General Practice[2], University Maastricht, Julius Centre for Primary Care and Health Sciences[3], Utrecht, The Netherlands.

15.10 Desmoid tumours in patients with Familial Adenomatous Polyposis (p. 57)
W.H. de Vos[1], A. Pikaar[2], A.E. de Jong[1], G. Griffioen[1], H.F.A. Vasen[1,2]. Dept of Gastroenterology, Leiden University Medical Center[1], The Netherlands Foundation for the Detection of Hereditary Tumours[2.]

15.20 Volume measurements of the anal sphincter complex using 3D transanal ultrasonography. (p. 58)
R.L. West , B.E. Hansen, E.J. Kuipers, R.J.F. Felt-Bersma. Dept of Gastroenterology and Hepatology, Erasmus MC/ University Medical Center, Rotterdam, The Netherlands.

15.30 Theepauze

Voorzitter: J.W. Greve

16.00 COX-2 expression and molecular alterations in Peutz-Jeghers hamartomas and carcinoma. (p. 59)
J.J. Keller[1], A.M. Westerman[2], W.J. de Leng[1], M.A.J. Weterman[1], H. van Dekken[2], J.H.P. Wilson[2], F.M. Giardiello[3], G.J.A. Offerhaus[1]. Dept of Pathology[1], Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands Depts of Internal Medicine and Pathology[2], University Hospital Rotterdam, Erasmus University, Rotterdam, The Netherlands, Dept of Medicine[3], The Johns Hopkins School of Medicine, Baltimore, MD, USA.

16.10 What is the added value of corpus biopsies to antral biopsies for the determination of H. pylori status? (p. 60)
M.C. van IJzendoorn[1], R.J.F. Laheij[1], J.B.M.J. Jansen[1] en W.A. de Boer[1,2]. Dept of Gastroenterology[1], University Medical Center St. Radboud, Nijmegen, Dept of Internal Medicine[2], Bernhoven Hospital, Oss, The Netherlands.

16.20 Local ablation methods in unresectable hepatic metastases of carcinoid tumours.
(p. 61) V. Meij[1], J.M. Zuetenhorst[2], R. van Hillegersberg[1], F. van Coevorden[1], R. Kröger[3], B.G. Taal[2]. Depts of Surgery[1], Gastroenterology[2] and Radiology[3], Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam.

16.30 Blastocystis hominis: commensal or pathogen? A double-blind, placebo-controlled study in children with recurrent abdominal pain.* (p. 62)
W.E. Tjon[1], A. Ten[1], G. Bocca, J.H. Hoekstra[2]. Dept Pediatrics, Maxima Medisch Centrum, Veldhoven[1], Dept Pediatrics Jeroen Bosch ziekenhuis s'-Hertogenbosch[2], The Netherlands.

16.40 Are drugs an underestimated (co)factor in the etiology of acute pancreatitis? (p. 63)
B.W.M. Spanier, M.J. Bruno. Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands.

16.50 Induction of rat hepatic and intestinal UDP-glucuronosyltransferases by naturally occurring dietary anticarcinogens. (p. 64)
E.M.J. van der Logt, H.M.J. Roelofs, F.M. Nagengast and W.H.M. Peters. Dept of Gastroenterology, University Medical Centre St Radboud, Nijmegen, The Netherlands.

17.00 Einde programma in deze zaal

17.00 **Voor de 'Guido Tytgat lecture' kunt u zich begeven naar de Brabantzaal**
'Mechanisms of liver injury in steatohepatitis'.
Dr. D. Pessayre, Hôpital Beaujon, Clichy, France.

17.30 Congresborrel / diner

Nederlandse Vereniging voor Hepatologie **Auditorium**

13.30 Ontvangst, inschrijving, koffie

Voorzitters: H. Moshage / R.H.J. Houwen

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

14.00 Sitosterolemia in ABCG5-null mice is aggravated upon activation of the liver X-receptor LXR (p. 65)
T. Plösch[1], V.W. Bloks[1], Y. Terasawa [2], S. Berdy[2], K. Siegler[2], F. van der Sluijs[1], I.P. Kema[1], A.K. Groen[3], B. Shan[2], F. Kuipers[1], M. Schwarz[2]. Center for Liver, Digestive and Metabolic Diseases[1], University Hospital Groningen, The Netherlands, Tularik Inc.[2], South San Francisco, CA, USA, Center for Experimental Hepatology[3], Academic Medical Center, Amsterdam, The Netherlands

14.10 Reduction of normothermic ischemia and reperfusion (I/R) injury of the liver after administration of interleukin-10 (IL-10) (p. 66)
S. Dinant[1], A.K. van Vliet[1], T.M. van Gulik[1]. Dept of Experimental Surgery[1], Academic Medical Centre, The Netherlands

14.20 Cystic fibrosis mice have an impaired capacity to dilute their bile, leading to increased cytotoxicity (p. 67)
F.A.J.A. Bodewes[1], M.J.C. Bijvelds[2], R. Havinga[1], J.F.W. Baller[1], H.R. de Jonge[2], H.J. Verkade[1]. Pediatric Gastroenterology, Dept Pediatrics[1], Academic Hospital, Groningen, Dept Biochemistry[2], Erasmus University, Rotterdam

14.30 Cyclosporin A inhibits bile salt synthesis rate and increases plasma triglycerides after liver transplantation in children (p. 68)
C.V. Hulzebos[1], F. Stellaard[1], F. Kuipers[1], R.Boverhof[1], T.Boer[1], V. Fidler[1], M.J.H. Slooff[2], P.M.J.G. Peeters[2], P.J.J. Sauer[1], C.M.A. Bijleveld[1], H.J. Verkade[1]. Dept Pediatrics and Dept Hepatobiliary Surgery, University Hospital, Groningen, The Netherlands

14.40 Improving the balance between apoptosis and regeneration in acute liver failure (Final report MLDS project WS 99-28) (p. 69-70)
M.H. Schoemaker, M. Homan, L. Conde de la Rosa, W. Gommans, P. Jansen, H. Moshage. Dept of Gastroenterology and Hepatology, University Hospital Groningen, the Netherlands

14.50 Impaired antigen presentation capacity and IFN-α production by dendritic cell populations of chronic hepatitis B patient (p. 71)
R.G. van der Molen, D. Sprengers, R.S. Binda, J. Kwekkeboom, J.G. Kusters, H.L.A. Janssen. Dept of Gastroenterology and Hepatology, Erasmus MC, Rotterdam, The Netherlands

15.00 Gallstones, gallbladder and gastrointestinal motility in β-thalassemia major (BTM) adults in southern Italy (p. 72)
P. Portincasa[1], A. Di Ciaula[3], A. Moschetta[1], M. Berardino[1], M. Giampaolo[1], A. Pietrapertosa[2], R. Cammarota[2], D. Campanale[2], N. Tannoia[2], G. Palasciano[1]. Section of Internal Medicine and Public Medicine (DIMIMP)[1], Section of Hematology, Dept Internal Medicine, Immunology & Infective Disease[2], University Medical School, Bari, Italy, Section of Internal Medicine[3], Hospital of Bisceglie, Bari, Italy

15.10 Inflammatory bowel disease after liver transplantation: the effect of immunosuppressive regimens (p. 73)
G.Dijkstra[1], A.P.van den Berg[1], J.H.Kleibeuker[1], M.J.H.Slooff[2], E.B.Haagsma[1]. Depts of Gastroenterology and Hepatology[1], and Hepatobiliary Surgery[2], University Hospital Groningen, The Netherlands

15.20 Liver preservation by hypothermic, pulsatile continuous perfusion using a new colloid-based perfusion solution (p. 74)
M. Bessems, B.M. Doorschodt, A.K. van Vliet, T.M. van Gulik. Surgical Laboratory Academic Medical Center, Amsterdam, the Netherlands

15.30 Theepauze

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

16.00 Hepatitis C Virus (HCV)-specific immunity after extracorporeal whole body hyperthermia in patients with chronic HCV infection (p. 75)
G.J. Boland[1], S. Pamporis-Moschatsis[1], C. Huijben[1], H. van Soest[2], A.M. van Loon[1], J. van Hattum[2]. Dept of Medical Microbiology and Virology[1] and Dept of Gastroenterology[2], University Medical Center Utrecht, The Netherlands

16.10 Viral dynamics during tenofovir therapy in patients with lamivudine-resistant hepatitis B mutants (p. 76)
A.A. van der Eijk[1], B.E. Hansen[2], H.G.M. Niesters[3], S.W. Schalm[1], R.A. de Man[1], Dept of Gastroenterology and Hepatology[1], Epidemiology and Biostatistics[2], Virology[3], Erasmus MC Rotterdam, the Netherlands

16.20 Pretreatment intrahepatic CD8+ cell number correlates with virological response to antiviral therapy in chronic hepatitis (p. 77)
J.M. Vrolijk[1], J. Kwekkeboom[1], H.L.A. Janssen[1], B.E. Hansen[1], P.E. Zondervan[2], A.D.M.E. Osterhaus[3], S. W. Schalm[1] and B.L. Haagmans[3]. Dept of Hepatology and Gastroenterology[1], Dept of Pathology[2], Institute of Virology[3], Erasmus MC, University Medical Center Rotterdam, The Netherlands

16.30 Mars treatment in posthepatectomy liver failure (p. 78)
M-P. van de Kerkhove[1], K.P. de Jong[2], A.M. Rijken[3], A.C.J.M. de Pont[4], T.M. van Gulik[1]. Depts of Surgery[1] and Intensive Care[4], Academic Medical Center, University of Amsterdam, Dept of Hepato-Pancreato-Biliary Surgery & Liver Transplantation, University Hospital[2], University of Groningen, Dept of Surgery, Amphia Hospital[3], Breda, The Netherlands

16.40 Doctor to patient transmission of hepatitis B: the problem and new solution (p. 79)
S.W.Schalm, E.H.C.J.Buster, A.A. van der Eijk, R.A. de Man. Dept Gastroenterology & Hepatology, Erasmus MC, Rotterdam, The Netherlands

16:50 Double needle biopsy of liver tumours; a new, safe and reliable technique (p. 80)
Bemelmans[1] MHA, J. Krissat[2], D. Castaing[3], D. Azoulay[3], H. Bismuth[3]. Dept of Surgery[1], Academic Hospital Maastricht, Hepatobiliairy and Pancreatic Surgical Center[2], Royal London Hospital, London, Hepatobiliairy and Liver Transplant Center[3], Paul Brousse Hospital, Villejuif-Paris, France

17.00 Einde programma in deze zaal

17.00 **Voor de 'Guido Tytgat lecture' kunt u zich begeven naar de Brabantzaal**
'Mechanisms of liver injury in steatohepatitis'.
Dr. D. Pessayre, Hôpital Beaujon, Clichy, France.

17.30 Congresborrel en aansluitend diner.

Nederlandse Vereniging voor Gastroenterologie, plenaire sessie **Brabantzaal**

Voorzitter: G.P. van Berge Henegouwen

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

20.00 High-fat enteral nutrition specifically decreases TNF-α and preserves gut barrier function in rats early after hemorrhagic shock (p. 81)
M.D.P. Luyer[1], M. Hadfoune[1], S. Konstantinov[3], J.A. Jacobs[2], C.H.C. Dejong[1], W.A. Buurman[1], J.W.M. Greve[1]. Depts of Surgery[1] and Medical Microbiology[2,3], University of Maastricht, University Hospital Maastricht and University of Wageningen[3], The Netherlands

20.15 The predictive value of intrahepatic CD8 T-lymphocytes and HBV core expression in relation to response to antiviral therapy for chronic hepatitis B patients (p. 82)
T.J. Tang[1], R.A. de Man[1], J.G. Kusters[1], J. Kwekkeboom[1], R.G. van der Molen[1], W.C.J. Hop[2], S.W. Schalm[1], H.L.A. Janssen[1]. Dept of Gastroenterology and Hepatology[1], Dept of Epidemiology and Biostatistics[2], Erasmus MC, Rotterdam

20.30 Whole body protein synthesis and breakdown are unchanged after major hepatectomy for malignancies in man (p. 83)
M.C.G. van de Poll[1], Y.C. Luiking[1], N. Dowidar[2], S.J. Wigmore[2], D.N. Redhead[3], O.J. Garden[2], M.W. de Haan[4], J.W.M. Greve[1], J.A. Ross[2], N.E.P. Deutz[1], K.C.H. Fearon[2], C.H.C. Dejong[1]. Depts of Surgery[1], Radiology[4], University Hospital Maastricht, Depts of Surgery[2], Radiology[3], Royal Infirmary, Edinburgh, Scotland

20.45 Germline mutations in the PRKCSH gene underly autosomal dominant polycystic liver disease (p. 84)
J.P.H. Drenth[1,2], R.H.M. te Morsche[1], R. Smink[1], J. Bonifacino[2], J.B.M.J. Jansen[1]. Dept of Gastroenterology and Hepatology[1], UMC St. Radboud, Nijmegen, The Netherlands and National Institutes of Health[2], Betesda MD, USA

21.00 **ALTANA-Lecture**
'Barrett's esophagus: etiology, epidemiology and genetics'.
Prof. A. Cameron, Mayo Clinic.

21.30 Ledenvergadering Nederlandse Vereniging voor Gastroenterologie.

22.00 Congresborrel in De Dommelpoort, aangeboden en gesponsord door AstraZeneca.

Casuistiek voor de klinikus **Brabantzaal**

Voorzitter: W. Hameeteman

09.00 Patiëntenbespreking

10.00 Einde programma

Sectie Gastrointestinale Endoscopie **Brabantzaal**

Voorzitter: W. Hameeteman

10.00 **De scoop op de richtlijn bloedingen**
presentatie Dr. R.J.L.F. Loffeld,
namens de commissie richtlijn tractus digestivus bloedingen

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

10.30 The role of endoscopic Doppler ultrasound in patients with peptic ulcer bleeding (p. 85) M.E. van Leerdam[1], E.A.J. Rauws[1], A.A.M. Geraedts[2], J.G.P. Tijssen[3], G.N.J. Tytgat[1]. Dept of Gastroenterology[1], Academical Medical Center, Dept of Gastro-enterology[2], Onze Lieve Vrouwe Gasthuis, Dept of Cardiology[3], Academical Medical Center, Amsterdam, The Netherlands

10.40 Digestive and systemic complications following oral ingestion of concentrated acetic acid or alkaline agent (p. 86)
J.W. Poley[1], E.W. Steyerberg[2], J. Dees[1], E.J. Kuipers[1], P.D. Siersema[1]. Dept of Gastroenterology and Hepatology[1], Dept of Public Health[2], Erasmus MC University Medical Center, Rotterdam, The Netherlands

10.50 Video capsule endoscopy in small bowel Crohn's disease (p. 87)
K.M.A.J. Tytgat, S.J.H. van Deventer, P. Fockens.
Dept of Gastroenterology, Academic Medical Center, Amsterdam, The Netherlands

11.00 *Koffiepauze*

Voorzitters: W. Hameeteman / H.M. van Dullemen

11.30 Long-term follow-up of the first ten patients treated with the gatekeeper reflux repair system (p. 88)
P. Fockens , A. Lei, M. Bruno, G. Boeckxstaens, G. Tytgat. Dept of Gastroenterology, Academic Medical Center, University of Amsterdam

11.40 MRI is a patient friendly and accurate alternative to ileocolonoscopy in determining disease activity in Crohn's disease. (p. 89)
J. Florie[1], D.W. Hommes[2], S.J.H. van Deventer[2], J.S. Laméris[1], J. Stoker[1]. Dept of Radiology[1] and Gastroenterology[2], AMC, Amsterdam, The Netherlands

11.50 Implications of routine endoscopic brush cytology in suspected biliopancreatic cancer: patient management and cost savings. (p. 90)
B.W.M. Spanier[1], E.A.J. Rauws[1], M. de Grauw[2], G.J.A. Offerhaus[2], S.J.H. van Deventer[1], M.J. Bruno[1]. Dept of Gastroenterology and Hepatology[1], Dept of Pathology[2], Academic Medical Center, Amsterdam, The Netherlands

12.00 Efficacy of Wallstents in benign biliary strictures due to chronic pancreatitis (p. 91)
A.M. van Berkel , D. van Westerloo, D. Cahen, J. Bergman, E. Rauws, K. Huibregtse, M. Bruno, Academic Medical Center, Dept of Gastroenterology, Amsterdam, The Netherlands

12.10 Malignant gastric outlet and duodenal obstruction - results of endoscopic stent insertion. (p. 92)
W. Stevens, H. Boot, B.G.Taal, A. Cats. Dept of Gastroenterology, Netherlands Cancer Institute, Amsterdam, the Netherlands

12.20 Long-term results of endoscopic drainage for biliary strictures due to chronic pancreatitis. (p. 93)
D.L. Cahen, D. Oskam, E.A.J. Rauws, A.M. van Berkel, G.N.J. Tytgat, K. Huibregtse, M.J. Bruno. Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands.

Nederlandse Vereniging voor Gastroenterologie **Baroniezaal**

Voorzitters: H. Verspaget / G. Dijkstra

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

09.00 Lack of Association between Toll-like receptor 4 haplotype and Asp299gly polymorphism and susceptibility for Inflammatory Bowel Disease (p. 94)
L.E. Oostenbrug[1], J.P.H. Drenth[2], I.J. Nolte[3], H.M. van Dullemen[1], G. van der Steege[3], D.J. de Jong[2], K. van der Linde[4], G. te Meerman[3], P.L.M. Jansen[1]. Dept of Gastroenterology and Hepatology[1], University Hospital Groningen, Dept of Gastroenterology and Hepatology[2], University Center St. Radboud, Nijmegen, Dept of Medical Genetics[3], University Hospital Groningen, Dept of Gastroenterology and Hepatology[4], University Medical Center Rotterdam, The Netherlands

09.10 IKBL+738 gene polymorfism is associated with high risk for colectomy in Ulcerative Colitis (p. 95)
R. Mallant-Hent[1], E. Gomez de la Concha[2], R. van Beem[2], B. de Vries[2], L. Fernandez Franco[2], A. van Bodegraven[1], A. Salvador Pena[1]. Free University Medical Center[1], Amsterdam, the Netherlands, Hospital Universitario Clinico San Carlos[2], Dept of Immunology, Madrid, Spain

09.20 The relevance of the TLR4 Asp299Gly gene polymorphism in the susceptibility to duodenal ulcers and severity of gastric antral inflammation (p. 96)
S.A. Morré, M.P. Bergman, E. Bloemena, H.W.M. Niessen, B.J. Appelmelk, C.M.J.E. Vandenbroucke-Grauls, A.S. Peña. VU University Medical Center, Amsterdam, The Netherlands

09.30 In Barrett's esophagus Muc4 and Muc6 can distinguish between high-grade dysplasia and normal columnar epithelium (p. 97)
D.A. Bax, E.J. Kuipers, J. Haringsma and J.G. Kusters. Dept of Gastroenterology and Hepatology, Erasmus MC, Rotterdam, The Netherlands

09.40 Cdx2 expression is an early marker for the development of Barrett's esophagus (p. 98) L.M.G. Moons, D.A. Bax, A.H.M. van Vliet, J. Haringsma, E.J. Kuipers, P.D. Siersema, J.G. Kusters, Dept of Gastroenterology and Hepatology, Erasmus MC, Rotterdam, The Netherlands

09.50 Mechanisms underlying mucosal tolerance in the gastro-intestinal tract (Final report MLDS-project) (p. 99)
J.N. Samsom, F. Hauet-Broere, W.W.J. Unger, J. Van Berkel and G. Kraal. Dept of Molecular Cell Biology, VU Medical Center, Amsterdam

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Sectie Experimentele Gastroenterologie **Baroniezaal**

Voorzitter: H. Verspaget / G. Dijkstra

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

10.00 Linkage analysis of colitis susceptibility in Gαi2 deficient mice unravel new loci in chromosomes not previously found in other models of experimental colitis. (p. 100)
M.E.A. Borm[1], JP. He[2], B.L Kensall[2], A.S. Peña[1], G. Bouma[1]. Vrije Universiteit Medical Centre[1], Amsterdam, The Netherlands, National Institutes of Health[2], Bethesda, USA

10.10 Mitogenic signaling in intestinal cells suppresses guanylyl cyclase C expression by phosphorylation of CDX-2 at serine 60* (p. 101)
E.H.H.M. Rings[1], M.D. Di Guglielmo[2], F. Boudreau[3], S. Kazerounian[2], I.A. Ruiz-Stewart[2], G.M. Pitari[2], S. Schulz[2], S.A. Waldman[2]. Dept of Pediatric Gastroenterology, Dept of Pediatrics[1] , Academic Hospital Groningen, Groningen, The Netherlands, Dept of Clinical Pharmacology, Depts of Medicine and Biochemistry and Molecular Pharmacology[2], Thomas Jefferson University, Philadelphia, USA and Dept. of Gastroenterology, Dept of Medicine[3], University of Pennsylvania, Philadelphia, USA

10.20 Dual role of Toll-like receptor (TLR)4 in septic peritonitis in mice: protection by TLR4 during initial infection is lost when peritonitis complicates acute pancreatitis (p. 102)
D.J. van Westerloo[1,2], S. Weijer[1], M.J. Bruno[2], S. Florquin[3], A.F. de Vos[1] and T. van der Poll[1]. Depts of Experimental Internal Medicine[1], Gastroenterology[2] and Pathology[3], Academic Medical Center, Amsterdam, The Netherlands

10.30 Opposite effects of phospholipid and cholesterol incorporation into bile salt micelles on ABCA1 and ABCG1 expression in CaCo2 cells: implications for intestinal cholesterol absorption (p. 103)
K.J. van Erpecum[1], A. Kosters[2], G.P. van Berge Henegouwen[1], A.K. Groen[2]. Dept of Gastroenterology[1] University Medical Center, Utrecht and Dept of Experimental Hepatology[2], Academic Medical Center, Amsterdam, The Netherlands

10.40 Helicobacter pylori is sensitive to nickel only at acidic pH (p. 104)
A.H.M. van Vliet, A. Heijens, S.W. Poppelaars, J. Stoof, E.J. Kuipers and J.G. Kusters. Dept of Gastroenterology and Hepatology, Erasmus MC, Rotterdam, The Netherlands

10.50 Identification of neurotensin binding sites. Neurotensin receptor-1 and -3 are expressed in human gastrointestinal tract (p. 105)
W.P. ter Beek, I. Biemond, E.S.M. Muller, M. van den Berg, C.B.H.W. Lamers. Dept of Gastroenterology-Hepatology, Leiden University Medical Center, The Netherlands

11.00 Koffiepauze

11.30 **INTERNATIONAL TEACHING SESSION**
'Apoptosis in Hepato-Gastroenterology'

Voorzitters: G. Dijkstra / J.G. Kusters

- Dr. Peter Möller, Institute of Pathology, University of Ulm, Germany
  "CD 95 ligand, TRAIL and their receptors in the gut: fictions and facts"

- Prof. dr. Dieter Häusinger, Klinik für Gastroenterology, Hepatology und Infektiologie Heinrich-Heine Universität, Düsseldorf, Germany
  "New aspects on apoptosis in the liver".

12.30 Lunchbuffet expositiehal

Nederlandse Vereniging voor Gastroenterologie **Zaal 80**

Voorzitters: C.M.F. Kneepkens / M. Sinaasappel

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

09.30 Quality of Life in children with inflammatory bowel disease: psychometric properties of the Dutch Impact questionnaire, coping strategies and parent-child differences (Final report MLDS-project)* (p. 106)
H.H.F. Derkx, H.J. van der Zaag-Loonen. Emma Children's Hospital Academic Medical Center, Amsterdam, the Netherlands

09.40 Predictors of outcome in children and adults with achalasia treated with pneumo-dilation; A prospective study* (p. 107)
P.Scholten[1], G.L. Ong[2], J. Bouquet[3], E.J. Kuipers[1]. Depts of Gastroenterology and Hepatology[1], Surgery[2] and Pediatrics[3], Erasmus University Medical Center, Rotterdam, the Netherlands

09.50 Functional defecation disorders in children (FGD's); the paediatric Rome-2 criteria revisited* (p. 108)
J. Heijmans, W.P. Voskuijl, J.A. Taminiau and M.A. Benninga. Dept of Paediatric Gastroenterology and Nutrition, Emma Childrens Hospital, Academic Medical Center, Amsterdam, The Netherlands

10.00 Celiac disease in the dutch general population (p. 109)
J.J. Schweizer[1], H.B. Bueno-de Mesquita[2], M.B. von Blomberg[3], C.J.J. Mulder[4], M.L. Mearin[1]. Dept of Paediatrics[1], Leiden University Medical Centre, Leiden, National Institute of Public Health and the Environment[2], Bilthoven, Dept of Pathology[3], Free University Medical Centre, Amsterdam, Dept of Gastroenterology[4], Rijnstate Hospital, Arnhem, The Netherlands

10.10 Medical audit on local results of infliximab (IFM) therapy for active Crohn's disease (CD) (p. 110)
W. Lesterhuis, R. Beukers, W. van de Vrie. Albert Schweitzer Ziekenhuis, Dordrecht, The Netherlands

10.20 Completion proctectomy after laparoscopic emergency colectomy for Inflammatory Bowel Disease: a comparative study (p. 111)
S. Maartense, M.S. Dunker, J.F. Slors, P. van Duijvendijk, D.J. Gouma and W.A. Bemelman. Dept of Surgery Academic Medical Center Amsterdam, The Netherlands

10.30 Efficacy and toxicity of 6-mercaptopurine in 30 patients with inflammatory bowel disease (p. 112)
L.P.L. Gilissen[1], L.J.J. Derijks[2], P.M. Hooymans[2], J.J.H.M. Lohman[2], L.P. Bos[1], P.J. Bus[3], W.L. Curvers[4], S.J.H. van Deventer[4], D.W. Hommes[4], L.G.J.B. Engels[1]. Depts of Gastroenterology[1] and Clinical Pharmacy[2], Maasland Hospital Sittard, Dept of Gastroenterology[3], St Laurentius Hospital, Roermond, Dept of Gastroenterology and Hepatology[4] , Academic Medical Centre, Amsterdam, The Netherlands

10.40 Maintenance treatment with 6-thioguanine over one year in IBD patients (p. 113)
D.J. de Jong[1], L.J.J. Derijks[2], L.P.L. Gilissen[2], L.G.J.B. Engels[2], P.M. Hooymans[2], A.H.J. Naber[1], C.J.J. Mulder[3]. Depts of Gastroenterology and Clinical Pharmacy, University Medical Center Nijmegen[1], Maaslandhospital Sittard[2], Rijnstate Hospital Arnhem[3], The Netherlands

10.50 No predictive value of TPMT genotyping for leukopenia or hepatotoxicity during azathioprine therapy in Inflammatory Bowel Disease (p. 114)
W.L. Curvers[1], L.J.J. Derijks[3], P. Stokkers[1], E. Vogels[1], J. de Gast[2], I. Pronk[1], A. van Kampen[2], S.J.H. van Deventer[1], D.W. Hommes[1]. Dept of Gastroenterology and Hepatology[1], Dept of Bio-informatics[2], Academic Medical Center, Amsterdam, Dept of Clinical Pharmacy[3], Maasland Hospital Sittard, The Netherlands

11.00 Koffiepauze

Vrijdag 21 maart 2003

Programma Vereniging van Maag-Darm-Leververpleegkundigen **Parkzaal**

09.30	Ontvangst en inschrijving
10.00	Opening door de voorzitter en ledenvergadering. Dhr. H. Welling, voorzitter VMDLV
10.20	Het ontstaan, voorkomen en de gevolgen van ondervoeding. Dhr. C. Coenen, Kern Staflid Methodiekontwikkeling & Onderzoek, staf Zorg UMC St. Radboud Nijmegen.
10.40	Wat is refeeding en hoe kan dit worden voorkomen? Dr. R. Timmer, MDL-arts, St. Antonius ziekenhuis Nieuwegein.
11.00	Koffiepauze
11.30	De noodzaak en de functie van het voedingsteam. Dhr. G. Bouman, verpleegkundige Voedingsteam, UMC St. Radboud Nijmegen.
11.50	TPV-Verpleegkundige; TPV-training Mw. R. Vissers, TPV-verpleegkundige, UMC St. Radboud Nijmegen.
12.15	Forumdiscussie
12.30	Lunch

Dutch Symposium on Chronic Hepatitis B and C: Virology and Therapeutic Options

Jointly organized by the Dutch Association for Hepatology (NVH) and the Dutch Working Group on Clinical Virology (NWKV) of the Dutch Association for Medical Microbiology (NVMM).

Chronic Hepatitis B

Chairmen:	A.C.M. Kroes and H.L.A. Janssen
09.30	Introduction: Some issues related to the virology of hepatitis B A.C.M. Kroes, Leiden
09.40	Virology of hepatitis B virus, diagnosis, viral variants, pathogenesis and epidemiology W. Jilg, Regensburg
10.10	Discussion
10.15	Consensus treatment of chronic hepatitis B infection R.A. de Man, Rotterdam
10.45	Discussion
10.50	Break
11.10	Introduction: Some clinical issues related to the treatment of chronic hepatitis B B. van Hoek, Leiden
11.20	Management of chronic hepatitis B in modern clinical practice F. Nevens, Leuven
11.50	Discussion
11.55	Contribution of molecular virology to the management of hepatitis B virus infections H.G.M. Niesters, Rotterdam
12.25	Discussion
12.30	Lunch

Vervolg Symposium Nederlandse Vereniging voor Hepatologie **Auditorium**

Chronic hepatitis C

Chairmen: B. van Hoek and G. Boland

13.30 Consensus treatment of chronic hepatitis C
J.T. Brouwer, Delft

13.50 Hepatitis C virus: prospects for a vaccine and new approaches to treatment
W.J.M. Spaan, Leiden

14.20 First results of therapeutic vaccination in patients with chronic hepatitis C
F. Nevens, Leuven

14.30 Discussion

14.35 Progress in the clinical management of hepatitis C
S. Zeuzem, Homburg/Saar

15.05 Discussion

15.10 Close

Sectie Maagdarmmotoriek **Zaal 80**

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

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

11.30 Comparison between gastric barostat and SPECT scanning to detect gastric relaxation (p. 115)
B.D. van den Elzen[1], R.J. Bennink[2], G.N. Tytgat[1], G.E. Boeckxstaens[1]. Dept of Gastroenterology[1] and Nucleair Medicine[2], Academic Medical Center, Amsterdam, The Netherlands

11.40 Relation of partial gastric volumes and upper gastrointestinal sensations in patients with functional dyspepsia and healthy volunteers measured with 3-dimensional ultrasonography (p. 116)
M.W. Mundt, A.J.P.M. Smout, M. Samsom, Gastrointestinal Research Unit. Depts of Gastroenterology and Surgery, University Medical Center, Utrecht, The Netherlands

11.50 The effect of subcutaneous pegylated recombinant native human leptin on gastric emptying in man. (p. 117)
M.A. van Nieuwenhoven[1], C.J. Hukshorn[2], R. Langeveld[2], W.H.M. Saris[2], R-J.M. Brummer[1]. Depts of Gastroenterology[1], University Hospital Maastricht and Human Biology[2], Maastricht University, the Netherlands

12.00 Redefining the lag phase for solids using 13C OBT and Doppler U (p. 118)
I.M. Minderhoud[1], M.W. Mundt[1], J.M.M. Roelofs[2], M. Samsom[1]. Dept of Gastro-enterology[1], University Medical Center Utrecht, the Netherlands, Dept of Surgery[2], University Medical Center Utrecht, the Netherlands

12.10 Does octreotide influence gastric motor and sensory function in functional dyspepsia? (p. 119)
E.A. van Hoboken, P.A. Verbeek, C. Penning, P.P.J. van der Veek, A.A.M. Masclee. Leiden University Medical Center, Leiden, The Netherlands

12.20 Influence of corticotrophin releasing hormone on gastric sensitivity and motor function in healthy volunteers (p. 120)
B.D. van den Elzen, G.N. Tytgat, G.E. Boeckxstaens. Dept of Gastroenterology, Academical Medical Center, Amsterdam, The Netherlands

12.30 Lunchbuffet expositiehal

Sectie Experimentele Gastroenterologie **Baroniezaal**

Voorzitters: H. Kusters / H.W. Verspaget

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

14.00 Acid- and metal-responsive transcriptional induction of ammonia-producing enzymes in Helicobacter pylori (p. 121)
A.H.M. van Vliet, S.W. Poppelaars, J. Stoof, A. Heijens, E.J. Kuipers and J.G. Kusters. Dept of Gastroenterology and Hepatology, Erasmus MC, Rotterdam, The Netherlands

14.10 Fibroblast-derived matrix metalloproteinases activate a potent neutrophil chemo-attractant from intestinal epithelial cells (p. 122)
L. Kruidenier[1], S.L.F. Pender[2], S. Naik[1], R. Mongrino[2], J. Collins[2], T.T. MacDonalds[2], I.R. Sanderson[1]. Dept of Adult and Paediatric Gastroenterology[1], Barts and The London, Queen Mary's School of Medicine and Dentistry, London, UK. Division of Infection, Inflammation, and Repair, School of Medicine[2], University of Southampton, UK

14.20 Hypoxia and reoxygenation primarily affect absorption relative to secretion, without changing barrier function in rat ileum *in vitro*. (p. 123)
I.G. Schoots, P.B. Bijlsma, G.I. Koffeman, T.M. van Gulik. Surgical Laboratory, Dept of Surgery, Academic Medical Centre, Amsterdam, The Netherlands

14.30 Basolateral Ca^{2+} -dependent K^+ -channels play a key role in Cl^- secretion from colon mucosa by taurodeoxycholate (TD) (p. 124)
A. Moschetta[1], P. Portincasa[1], L. Debellis[2], M. Petruzzelli[1], R. Montelli[1], P. Gustavsson[1], G. Palasciano[1]. Dept of Internal and Public Medicine[1], Section of Internal Medicine, Dept of General and Environmental Physiology[2], University of Bari, Italy

14.40 Leucocyte matrix metalloproteinase (MMP)-9 gene and protein regulation in Crohn's disease (p. 125)
Q. Gao, J.M. van der Zon, W. van Duijn, M.J.W. Meijer, R.A. van Hogezand, C.B.H.W. Lamers, H.W. Verspaget. Dept Gastroenterology-Hepatology, LUMC, Leiden, The Netherlands

14.50 Cervical vagotomy aggravates experimental pancreatitis severity in mice (p. 126)
D.J. van Westerloo[1,2], M.J. Bruno[2], S. Florquin[3] , A.F. de Vos[1] and T. van der Poll[1]. Depts of Experimental Internal Medicine[1], Gastroenterology[2] and Pathology[3], Academic Medical Center, Amsterdam, The Netherlands

15.00 Of Mice and Man: Common H+,K+-ATPase T-cell epitopes in human and murine autoimmune gastritis (p. 127)
M.P. Bergman[1], A. Amedei[2], M.M. D'Elios[2], A. Azzurri[2], M. Benagiano[2], C.Tamburini[2], R. Van der Zee[3], C.M. J. E. Vandenbroucke-Grauls[1], B.J. Appelmelk[1], G. Del Prete[2]. Dept of Medical Microbiology and Infection Control[1], VU University Medical Center, Amsterdam, The Netherlands; Dept of Internal Medicine[2], University of Florence, Florence, Italy, Dept of Infectious Diseases and Immunology[3], Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands

15.10 Methotrexate and Infliximab act synergistic by inducing enhanced apoptosis in activated human lymphocytes (p. 128)
J.M.H. van den Brande[1], H. Braat[2], Chr.A. Bauer[2], M. Peppelenbosch[2], S.J.H. van Deventer[1], D.W. Hommes[1]. Dept of Gastroenterology[1], Dept of Experimental Internal Medicine[2], Academic Medical Center, Amsterdam, The Netherlands

15.20 Physiological consequences of short bowel syndrome in a piglet-model* (p. 129)
G.I. Koffeman, I.G. Schoots[1], D.C. Aronson, J.A.J.M.Taminiau[2], P.B. Bijlsma[2], T.M.van Gulik[1], H.A. Heij, W.G. van Gemert. Pediatric Surgical[1] Center Amsterdam AMC/VUMC, Surgical Laboratory, Dept of Pediatrics[2] Academic Medical Center, Amsterdam

15.30 The Aqua porin-8 water channel (AQP8) is largely distributed in rat gastrointestinal locations where large quantities of fluid are absorbed or secreted (p. 130)
G. Calamita[1], A. Mazzone[1], G. Cassano[1], P. Gena[1], D. Thomas[2], P. Portincasa[3] , M. Svelto[1]. Dept of General and Environmental Physiology[1], University of Bari, Bari, Italy URA CNRS 256, University of Rennes 1[2], Rennes, France, Section of Internal Medicine and Public Medicine (DIMIMP)[3], University Medical School, Bari, Italy

15.40 Troglitazone reduces fibrosis formation and progression in an experimental model of chronic pancreatitis in mice (p. 131)
D.J. van Westerloo[1,2], M.J. Bruno[2], S. Florquin[3], A.F. de Vos[1] and T. van der Poll[1]. Depts of Experimental Internal Medicine[1], Gastroenterology[2] and Pathology[3], Academic Medical Center, Amsterdam, The Netherlands

15.50 Identification of Fur- and iron-regulated genes of Helicobacter pylori using whole-genome DNA array analysis (p. 132)
F.D. Ernst[1,2,3], J. Stoof[1], B. Waidner[3], A.H.M. van Vliet[1], M. Kist[3], J.G. Kusters[1], S. Bereswill[3] and G. Homuth[2]. Dept of Gastroenterology and Hepatology[1], Erasmus MC, Rotterdam, The Netherlands, Institute of Microbiology and Molecular Biology[2], University of Greifswald, Greifswald, Germany, Institute of Medical Microbiology and Hygiene[3], University Hospital of Freiburg, Freiburg, Germany

16.00 Einde programma

Sectie Maagdarmmotoriek **Zaal 80**

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

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

14.00 Are transient lower esophageal sphincter relaxations (TLESRs) the most important mechanism of acid reflux exposure time in patients with gastroesophageal reflux disease (GERD)? (p. 133)
R.C.H.Scheffer[1], E.B. Wassenaar[1], M.A. van Herwaarden[1], R.H. Holloway[2], M. Samsom[1], A.J.P.M. Smout[1], H.G. Gooszen[1], L.M.A. Akkermans[1]. Gastrointestinal Research Unit, Depts of Gastroenterology and Surgery[1], University Medical Center Utrecht. Dept of Gastroenterology[2], Royal Adelaide Hospital, Adelaide, South Australia

14.10 The effect of Barrett's mucosa ablation with argon plasma coagulation (APC) on esophagogastric junction (EGJ) function. (p. 134)
R.C.H.Scheffer[2], J.R. Vermeijden[2], M.H. Otten[2], C.D. Kooyman[2], M. Samsom[1], H.G. Gooszen[1]. Gastrointestinal Research Unit, Depts of Gastroenterology and Surgery[1], University Medical Center Utrecht. Depts of Medicine and Pathology[2], Meander Medical Center, Amersfoort, The Netherlands

14.20 Effects of growth hormone deficiency and recombinant growth hormone therapy on postprandial gallbladder motility and cholecystokinin release. (p. 135)
A. Moschetta[1,3], Th.B. Twickler[2], J.F. Rehfeld[4], N.A.M. van Ooteghem[1], M. Castro Cabezas[2], P. Portincasa[3], G.P. van Berge Henegouwen[1], K.J. van Erpecum[1]. Depts of Gastroenterology[1] and Endocrinology[2], University Medical Center Utrecht, The Netherlands, Dept of Internal and Public Medicine, Section of Internal Medicine[3], University Hospital Bari, Italy, Dept of Clinical Biochemistry, University Hospital Copenhagen, Denmark[4].

14.30 Studies on the role of splanchnic innervation in visceral hypersensitivity associated with functional bowel disorders (Final report MLDS-project) (p. 136)
S.D. Kuiken, G.N. Tytgat, G.E. Boeckxstaens. Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam.

14.40 Visceral perception health: Role of the N-methyl-D-aspartate (NMDA)-receptor
(p. 137) S. Kuiken, S. van den Berg, G. Tytgat, G. Boeckxstaens. Academic Medical Center, Amsterdam, The Netherlands.

14.50 Lowered serotonergic activity changes cortical activation during painful rectal stimuli. (p. 138) M.A. van Nieuwenhoven[1], T.O.C. Kilkens[2], R-J.M. Brummer[1], W. Backes[3]. Depts of Gastroenterology[1], Psychiatry & Neuropsychology[2] and Radiology[3], University Hospital Maastricht, the Netherlands.

15.00 Does a rectal barostatprocedure induce stress in IBS patients and healthy subjects? (p. 139) M.L.J.E. Paffen[1], T.O.C. Kilkens[1], A. Honig[1], R.J.M. Brummer[2], M.A. van Nieuwenhoven[2]. Depts of Psychiatry and Neuropsychology[1] and Gastroenterology[2], University Hospital Maastricht, the Netherlands.

15.10 Irritable Bowel Syndrome in Ulcerative Colitis (p. 140)
J.J.L. Haans, P.P.J. van der Veek and A.A.M. Masclee. Dept of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands.

15.20 IBS patients have a slower rectal adaptive relaxation than healthy controls, not related to serotonergic activity (p. 141)
T.O.C. Kilkens[1], N. Vogelzangs[1], A. Honig[1], R.J.M. Brummer[2], M.A. van Nieuwenhoven[2]. Depts of Psychiatry and Neuropsychology[1], and Gastroenterology[2], University Hospital Maastricht, the Netherlands.

15.30 Is rectal motor and sensory dysfunction in Irritable Bowel Syndrome subtype specific (p. 142) P.P.J. van der Veek, A.A.M. Masclee. Dept of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands

15.40 The involvement of interstitial cells of cajal in the rectoanal inhibitory reflex* (p. 143)
F. de Lorijn[1], W.J. de Jonge[2], M.A. Benninga[1], G.E. Boeckxstaens[2]. Dept of Pediatric Gastroenterology and Nutrition[1], Emma Children's Hospital, Dept of Gastroenterology and Hepatology[2], Academic Medical Center, Amsterdam, The Netherlands

15.50 PEG 3350 compared to lactulose in the treatment of paediatric constipation. A double-blind, randomized controlled trial* (p. 144)
W. Voskuijl[1], F. de Lorijn[1], W. Verwijs[2], P. Hogeman[3], J. Heijmans[1], J. Taminiau[1] and M. Benninga[1]. Dept of Paediatric Gastroenterology and Nutrition[1], Emma Childrens Hospital, Academic Medical Center, Amsterdam, Dept of Paediatrics[2], Hofpoort Ziekenhuis, Woerden, Dept of Paediatrics[3], Meander Medisch Centrum, Amersfoort
The Netherlands

16.00 Einde programma

Sectie Endoscopie Verpleegkundigen en Assistenten **Brabantzaal**

13.30 Algemene ledenvergadering SEVA

14.00 Dr. R.A. van Hogezand, MDL arts LUMC
Anti-TNF, behandeling en resultaten bij M. Crohn.

14.30 Mw. dr. M. van Bokhorst, dienst diëtetiek VUMC:
Voeding en ondervoeding in het ziekenhuis

14.50 Dr. R.A. de Man, MDL-arts, Erasmus MC Rotterdam
Hepatitis A virusinfectie

15.10 Theepauze

15.30 Dhr. A. Patty, verpleegkundig consulent, hepatologie VUMC.
Het verpleegkundig spreekuur hepatologie

15.50 Prof. dr. C.J.J. Mulder, MDL-arts, VUMC Amsterdam
Pre-lymfomen bij coeliakie

16.10 Einde programma

Revision of previously undefined gastrointestinal mesenchymal tumors results in a high rate of actual stromal (GIST) tumors.

H.J.P. de Schipper, LNN; R.S.L. Liem, H.F.G.M. van den Ingh and E. van der Harst. MCRZ, Locatie Clara, Rotterdam.

Treatment of gastrointestinal stromal tumors (GIST) has been revolutionary changed by the recent development of tyrosinekinase inhibitors. Imatinib has been shown to be highly effective in the treatment of GIST metastases, recurrences and irresectable tumors. In this light discriminating GISTs from other mesenchymal tumors has important implications for follow-up and adjuvant chemotherapy. GISTs can be accurately diagnosed by immunoperoxidase staining with the marker CD117, which can also be applied on archival formalin fixed material. Therefore, all cases of previously resected mesenchymal tumors of the gastrointestinal tract in a single institution were reviewed for accuracy of diagnosis with this recently developed immunohistochemical marker.
In the period 1987-2002 20 men and 18 women were operated for gastrointestinal mesenchymal tumors. Mean age was 75 year (range 41-100). Diagnosis was originally based on the histological type, cell shape, prevalence of mitotic figures and rarely peroxidase staining. In 24 of 38 patients the tumor was located in the stomach, in 7 it was in the small bowel, in 4 in the colon, in 2 in the esophagus and in 1 in the retroperitoneal space. Originally, lacking the CD117 marker, in only 6 patients GIST had been correctly diagnosed. Of the remaining 32 patients 22 cases (69%) proved to have been actually operated for a CD117 positive GIST.
Conclusion: Clinical diagnoses of archival mesenchymal tumors of the gastrointestinal tract should be reviewed with modern immunohistochemical markers for accuracy of diagnoses, considering the therapeutical consequences.

Surgical management of ampullary tumours: local or extensive resection

S.M.M. de Castro, N.T. van Heek, O.R.C. Busch, T.M. van Gulik, H. Obertop, D.J. Gouma. Dept. of Surgery, Academic Medical Centre Amsterdam, The Netherlands

Tumours of the ampulla of Vater are relatively uncommon and have a better 5-year survival than other periampullary tumours. Controversy exists which tumours (adenomas vs. adenocarcinomas) need resection by local or extensive procedures. This study was conducted in order to evaluate whether local resection is recommended. We retrospectively evaluated 128 patients (1992-2001). Preoperative clinical data, peroperative findings, and the outcome after surgery were scored. Survival analysis was performed using the Kaplan-Meier method.
The mean age was 65 years (74 male and 54 female). Local resection was performed on 16 patients with preoperative suspected adenoma of the ampulla of Vater. Nine patients (46%) could suffice with local resection after laparotomy, and 7 patients (44%) appeared to have an ampullary carcinoma and underwent subsequent pancreaticoduodenectomy. The remainder of the group (n=112) underwent an elective pancreaticoduodenectomy for suspected ampullary tumours. Pathology found ampullary adenocarcinoma (n=104), adenoma (n=4), other malignant tumours (n=3) and focal pancreatitis (n=1). Mortality occurred in 1 of the 9 patients (11%) after local resection and in 5 of the 119 patients (4.2%) who underwent pancreaticoduodenectomy. Patients (n=53) who had at least 5-year follow-up had a median survival of 50.3 months and 5-year survival 48%. No recurrence occurred after local resection. One hundred of the 119 patients (84%) who underwent a pancreaticoduodenectomy had a R0 resection.
Conclusion: Despite preoperative staging, 44% of the patients who underwent local resection for adenoma needed a second extensive resection because malignancy was found. Local resection is considered an adequate surgical treatment for patients with adenomas but during surgery frozen section should be taken to exclude malignancy. A pancreaticoduodenectomy is treatment of choice in patients with carcinoma; the 5-year survival rate was 48.

Prospective randomized controlled multi-center trial evaluating prophylactic gastrojejunostomy for unresectable pancreatic head cancer - Interim analysis -

N.T. van Heek[1], S.M.M. de Castro[1], R.C.I van Geenen[1], E.J. Hesselink[2], T.C.K. Tran[3], G. Kazemier[3], P.J. Breslau[4], O.R.C. Busch[1], H. Obertop[1], D.J. Gouma[1]. Dept. of Surgery, Academic Medical Center Amsterdam[1], Hospital Gelre Apeldoorn[2], Apeldoorn, University Hospital Dijkzigt[3], Rotterdam, Hospital Rode Kruis[4], The Hague, The Netherlands

Controversy still exists if a prophylactic gastrojejunostomy should be performed routinely. The aim of this randomized study was to evaluate the role of a prophylactic gastrojejunostomy in patients with unresectable periampullary carcinoma. Between December 1998 and March 2002, 70 patients who underwent exploration to perform a PPPD were proven to have unresectable disease and were randomized to receive a hepaticojejunostomy and a retrocolic gastrojejunostomy, or a hepaticojejunostomy alone. Randomization was stratified for center and metastases. Primary endpoints were development of clinical gastric outlet obstruction (GOO) and therapeutic intervention. Secondary endpoints were mortality, morbidity, hospital stay, survival and quality of life. Five patients were excluded due to revision of the pathology or missing follow-up. From the remaining 65 patients, 36 patients underwent a double, and 29 a single bypass. Clinical GOO was found in 2/36 (5.5%) patients with a double bypass, and in 12/29 (41.4%) patients with a single bypass (p=0.001). In the double bypass group one patient (2.8%) and in the single bypass group 6 patients (20.7%) required gastrojejunostomy (p=0.04). The median time between initial exploration and late gastrojejunostomy was 3.5 months. Postoperative morbidity rates, including delayed gastric emptying, were 31% in the double versus 28% in the single bypass group. The postoperative length of stay was 16.0 days in the double versus 10.5 days in the single bypass group (p=0.003). Mean survival was 8.0 months in the double versus 10.1 months in the single bypass group (p=ns).
Conclusions: Prophylactic gastrojejunostomy significantly decreases the incidence of GOO. However, it is associated with prolonged hospital stay. This study confirms that a prophylactic gastrojejunostomy should be performed routinely in patients undergoing surgical palliation for an unresectable periampullary tumor.

Hospitalization (readmission) after surgical treatment of patients with pancreatic adenocarcinoma

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

The prognosis of patients with pancreatic carcinoma is poor, even after surgical treatment. Therefore, quality of life is a cornerstone in the evaluation of outcome. Hospital free survival and readmission rates are important variables that influence the quality of life. The aim of this study was to evaluate readmissions after surgical treatment for pancreatic adenocarcinoma.
From January 1992 to January 2002, 343 patients underwent surgical treatment for pancreatic adenocarcinoma, of which 164 patients a pancreaticoduodenectomy (PD) and 179 patients a bypass (BP). Five patients died during initial hospitalization after BP (none after PD) and were excluded. Readmissions were divided in 6 categories. Those required for early surgical complications within four weeks after the initial discharge, those for chemo/radiotherapy, those for long term complications related to surgery, those for progressive disease, those for terminal care and those for other indications.
A high percentage (59%) of patients was readmitted, 99 (61%) after PD and 101 (57%) after BP. The 390 readmissions registered were equally distributed over the two groups. Median hospital stay of each readmission was 7 and 3 days after PD and BP respectively. After PD 0.69% of the total survival time after initial discharge was spent in a hospital, after BP 0.47% (ns).
Readmissions for early complications were required in 2% and 1%, for chemo/radiotherapy in 12% and 13%, for long term complications in 19% and 6%, for progressive disease in 54% and 67%, for terminal care in 1% and 7% and for other indications in 11% and 7% after PD and BP respectively.
Surgical treatment of patients with pancreatic carcinoma is associated with a substantial readmission rate, although the total hospital stay after initial discharge was less than 1 per cent of the postoperative survival time. Long term complications and in particular progressive disease were the most important reasons for readmission.

Ex vivo sentinel node procedure in patients with colorectal carcinoma; a feasible technique

A.A.W. van Geloven[1], E.G.J.M. Pierik[1], F.C.P. Moll[2], J.E. Boers[2]. Dept of Surgery[1], and Pathology[2], Isala Klinieken (loc. Weezenlanden), Zwolle, The Netherlands

Distant metastasis develops in 30% of patients with colorectal carcinoma after initial negative lymph node status. With the sentinel node (=SN) technique possible micrometastases can be detected. These patients may benefit from adjuvant chemotherapy. The aim of this study is to evaluate the feasibility of the ex vivo technique. Methods, technical problems and results are described.
During 1 year 47 consecutive patients (23 M, 24 F) with colorectal carcinoma were included; the ex vivo SN procedure was performed on all resection specimens. After initial practical problems and adjustments in 13 specimens, a standardized procedure was carried out on the next 34. After resection, the antimesenterial side of the colon was opened and Patent blue dye was injected in the submucosa at short distance to the tumour. After local massage, blue lymphtracts and SNs were identified and submitted for pathological investigation. One H&E stained slide was read of each SN, followed by 2-level immunohistochemical staining for both H&E and low molecular weight cytokeratins.
In the first 13 patients only 3 SNs could be identified. In the next 34 (with the standardized technique), 1 specimen failed to reveal lymph nodes. SNs were identified in all Dukes C carcinoma patients (n=11), 7/11 of these nodes were tumour negative representing false negative SNs. In the group of Dukes A or B carcinoma patients (n=22) SNs were detected in 21 (95%). After immunohistochemical investigation, 15 SNs remained tumour-negative, 5 contained isolated tumour cells, and 1 revealed on sectioning a metastasis.
Conclusion: The ex-vivo SN technique in patients with colorectal carcinoma is a fast, safe and feasible technique. In 95% of Dukes A and B patients a SN could be identified; one patient was upstaged from Dukes B to C. The colorectal ex vivo SN procedure seems a promising technique; a more accurate staging can be achieved, possibly contributing to improvement of treatment and survival-rates in the future.

Disturbances in fecal continence after Transanal Endoscopic Microsurgery (TEM)

L.P.S. Stassen, T. Karsten. Dept. of Surgery, Reinier de Graaf Groep, Delft/Voorburg, The Netherlands

With TEM benign or T1 well or moderately differentiated malignant rectal tumors of up to 10 cm in diameter, and till 20 cm from the anal verge can be locally resected.
Its advantages are low recurrence-, morbidity- and mortality rates.
A matter of concern is postop fecal incontinence, due to the use of a 4 cm diameter rectoscope. Mild incontinence with full recovery after one year has been reported.
To further investigate this a prospective study was conducted. Anal sfincter function and -integrity were evaluated using Parks' grading of incontinence to which 'urge' was added, manometry and endorectal ultrasound (< 2001) or -MRI (≤ 2001) preop and at 3 months and 1 year postop.
Till January 2003 66 patients were included. In 5 patients conversion to a transabdominal-, or classical transanal approach was performed. Only the results of the patients who underwent TEM are reported.
Urge was present in 15% of pts preop, 34% at 3 mths and 25% at 1 yr postop; grade 2 incontinence in 27, 16 and 7%; grade 3 in 9, 2 and 4%. Recently developed preop incontinence may be due to the tumor. It is important to note that in 41% of pts at 3 mths and 21% at 1 yr continence was inferior to longer than 1 yr preop.
Manometry in 56 pts preop, 39 at 3 mths, and 23 at 1 yr revealed internal sfincter pressures at these moments of 62, 48 and 50 mmHg, and external pressures of 145, 133 and 138. In patients measured at all 3 moments these values were 59, 44 and 49 for internal- and 122, 124 and 129 for external pressure.
Endorectal ultrasound or -MRI obtained preop, at 3 mths and 1 yr in 46, 30 and 19 pts, detected atrophy preop in 1 patient, and a defect postop in another in whom the sfincter had been partially resected with the specimen.
Conclusion: in contrast to previous reports disturbances in fecal continence after TEM do not fully recover after one year. In a minority of patients mild incontinence persists which seems to be due to internal anal sfincter dysfunction.

Sacral Nerve Stimulation for fecal incontinence

S. Koch, Ö. Uludag, W. van Gemert, C. Baeten, Academic Hospital Maastricht, The Netherlands.

Sacral nerve stimulation is well known for urinary incontinence. The effect on fecal incontinence is also remarkable. Indications for inclusion were: severe fecal incontinence of more than once a week, intact anal sphincters and failure of conservative treatment.
All patients underwent preoperatively anal manometry, endosonography, pudendal latency times, defecography and a 3 week baseline diary. All patients underwent peripheral neural evaluation (PNE). When at PNE a decrease of at least 50 percent of incontinence episodes were seen at a 3 weeks diary, the patients were eligible for SNS implant.
61 Patients (49 women) with a mean age of 55 years were included. In 59 patients PNE was possible to perform. 49 out of 59 (83%) of the patients had a successful PNE. Of these patients, 47 underwent permanent implantation and 2 patients are on the waiting list for implant. The average number of incontinence episodes decreased from 9,8 per week to 1,2 per week and this results maintained the same during a follow-up of one year. No change in resting and squeeze pressure was seen. Complication rate was low and only in 2 patients the device had to be explanted.
Conclusion: SNS is a feasible treatment option for fecal incontinent patients with an intact sphincter.

Health status and quality of life after Ileo Neo Rectal Anastomosis (INRA) in comparison to Ileo Pouch Anal Anastomosis (IPAA)

W.Hueting[1], J. de Vries[2], C.J.H.M.van Laarhoven[3], H.G. Gooszen[1]. Dept. of Surgery[1], University Medical Centre Utrecht, Dept of Psychology[2], Tilburg University, Dept. of Surgery[3], St. Elisabeth Hospital, Tilburg, The Netherlands

Restorative surgery after proctocolectomy is typical “quality of life surgery”. The early results of the Ileo Neo Rectal Anastomosis (INRA) as an alternative restorative procedure to the Ileo Pouch Anal Anastomosis (IPAA) are promising in terms of procedure related complications. It is unclear whether these results are also reflected in Quality of Life (QOL). This study was designed to compare the outcome of INRA and IPAA in terms of health status, disease-specific symptoms and QOL assessed not only by established tests but also by a new tool, the WHOQOL 100.
All postoperative INRA patients with a follow-up longer than one year were included in this study. Patients were asked to complete a disease-specific (IBDQ) and a generic (SF-36) health status questionnaire, a generic QOL (WHOQOL-100), and two symptom questionnaires (e.g., Vaizey). 108 IPAA patients, members of the Dutch Society for Ulcerative Colitis and Crohn Patients (CCUVN), served as the reference group.
24/27 INRA patients (median age: 33.3 years, 16 men) returned the questionnaires. Apart from a lower score of the facet ‘sleep and rest’, no differences were found INRA and IPAA. Chronic pouchitis, reclassification to Crohn’s Disease (CD) and high defecation frequency (>10/day), did not affect QOL and health status, except for the domain ‘bowel function’ of disease-specific health status resulted in lower values ($p<0.01$) for the INRA subgroup with these complications. Variation in Vaizey score and length of follow-up did not lead to changes in generic health status, disease-specific health status and QOL.
Conclusion: Also with respect to QOL and health status is INRA an equivalent alternative. Subgroup analysis of complicated INRA patients failed to show a difference, probably due to a type II error.

Does experience influence outcome of laparoscopic Nissen fundoplication?

R.K.J. Simmermacher[1], H.J.M. Oostvogel[2], P.J.J. van Rijn[3], M.A. Cuesta-Valentin[4], J.J.B van Lanschot[5], L.P. Stassen[6], H.G. Gooszen[1]. Dept. of Surgery[1], University Medical Center Utrecht, Dept. of Surgery[2], St. Elisabeth Hospital, Tilburg, Dept. of Surgery[3], 't Lange Land Hospital, Zoetermeer, Dept. of Surgery[4], VU Medical Center, Amsterdam, Dept. of Surgery[5], Academic Medical Center, Amsterdam, Dept. of Surgery[6], Reinier de Graaf Gasthuis, Delft, The Netherlands

Introduction: In 2000 the Netherlands Antireflux Surgery Study Group published a randomized trial comparing the laparoscopic and conventional Nissen fundoplication for gastroesofageal reflux disease (GERD) revealing, a signifcantly worse outcome in the laparoscopic group. Criticism focused on an alleged lack of experience among the laparoscopic surgeons in general and specifically with the Nissen-fundoplication. Therefore the protocol concerning the laparoscopic approach was changed and strict demands on experience of the surgical team were postulated after which a new cohort study was performed.
Materials and Methods: A consecutive cohort of 100 patients was included in this trial, performed in 6 different hospitals. The protocol demanded a surgical team of two surgeons from the participating hospitals both of whom should have done more than 15 Nissens. All operations were videorecorded. Primary endpoints were dysphagia, recurrent GERD or intrathoracic herniation at three months postoperatively necessitating re-operation.
Results: Within a 24 month period 121 patients were included and operated according to the protocol. Within four months postoperatively 3 patients (2,5%) had to be reoperated due to telescoping in two cases and too tight a plication in one patiënt.
Discussion: With the same endpoints and the same surgeons as in Manchet I significantly better initial results have been obtained. The difference of reoperations three months after a laparoscopic Nissen fundoplication when comparing this study to the previously performed one, 2% versus 19%, suggests that the surgical team performing a laparoscopic fundoplication should meat certain prerequisites in order to guarantee a resonable result in the short term. It appears that the Nissen shows a learning curve which of course might be different for individual surgeons but for a dedicated team of surgeons consists of at least > 30 performed operations.

The role of NOS-2 and NOS-3 in renal and muscle protein metabolism during early endotoxemia in mice

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Previously, we observed an enhanced renal protein synthesis in the early response to endotoxemia in wild-type mice (Hallemeesch et al, AJP 2002;282:F316-23). Whether this anabolic function of the kidney is regulated by nitric oxide (NO) is unknown. Therefore, the present study was aimed at determining the role of the NO-synthesizing enzymes NOS-2 (iNOS) and NOS-3 (ecNOS) in renal protein metabolism after endotoxin treatment in mice, as a model of early sepsis.
Renal protein metabolism was measured in the early phase of endotoxin treatment (100mg/200ml saline/10g LPS) in C57BL6/J (WT), NOS2-KO and NOS3-KO female mice (8-9 mice/group). Protein metabolism was measured five hours after LPS or saline (Control) in renal venous and arterial catheterized mice under anesthesia, using stable isotopes of phenylalanine (L-[ring-2H5]phe) and tyrosine (L-[ring-2H2]tyr). Renal blood flow was measured using radioactive PAH extraction. Phe consumption and production by the kidney were calculated from arterio-venous (AV) differences in concentration and tracer-tracee ratio of phe. Hydroxylation was calculated as the conversion of phe to tyr. Net protein synthesis (PS) is based on AV-differences in phe concentration, measured across the kidney. Significance was tested using 2-way ANOVA.
After LPS challenge, renal phe consumption increased in all 3 groups: from 7±2 to 17±3 nmol/10g/min in WT, from 8±3 to 26±7 nmol/10g/min in NOS2-KO, and from 7±1 to 18±6 nmol/10g/min in NOS3-KO ($P<0.001$, LPS vs Control). After LPS, both PS and phe hydroxylation were increased in all groups ($P<0.01$, LPS vs Control). Phe production also increased after LPS in all groups, but to a lesser extent than phe consumption, resulting in an enhanced net PS after LPS in all groups: 12±2 vs 4±3 nmol/10g/min (WT), 11±2 vs 8±3 nmol/10g/min (NOS2-KO), and 13±5 vs 4±1 nmol/10g/min (NOS3-KO)($P<0.01$ for LPS vs Control).
Conclusion: Stimulated renal protein synthesis in early endotoxemia appears to be independent of NO.

NOS-3 has a role in muscle protein metabolism after endotoxin treatment in mice

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Muscle wasting occurs in prolonged sepsis. Changes in muscle kinetics in early sepsis and the involvement of the nitric oxide (NO) synthesizing enzymes NOS-2 and NOS-3 in this process are unknown. Therefore, this study was aimed at determining the role of the NO-synthesizing enzymes NOS-2 (iNOS) and NOS-3 (ecNOS) in muscle protein metabolism after endotoxin treatment in mice, as a model of early sepsis.
Hindquarter muscle protein metabolism was measured in the early phase of endotoxin treatment (100mg/200ml saline/10g LPS) in C57BL6/J (WT), NOS3-KO and NOS2-KO female mice (8-9 mice per group). Muscle protein metabolism was measured five hours after LPS or saline (Control) in caval venous and carotid arterial catheterized mice under anesthesia, using a stable isotope of phenylalanine (L-[ring-2H5]phe). Hindquarter blood flow was measured using radioactive PAH extraction. Phe consumption and production were calculated from arterio-venous (AV) differences in concentration and tracer-tracee ratio of phe, measured across the muscle. Phe flux or net balance is based on AV-differences across the muscle in phe concentration. Significance was tested using 2-way ANOVA.
After LPS challenge, muscle phe consumption (mainly protein synthesis), increased in WT and NOS2-KO mice ($P<0.05$), but not in NOS3-KO mice (LPS vs Control: 13±3 vs 8±1 nmol/10g/min (WT), 15±5 vs 7±2 nmol/10g/min (NOS2-KO), and 9±4 vs 10±2 nmol/10g/min (NOS3-KO)). Phe production (protein breakdown) tended to increase with LPS ($P=0.06$, LPS vs Control) in WT (13±2 vs 9±1 nmol/10g/min) and NOS2-KO mice (15±5 vs 8±2 nmol/10g/min), but not in NOS3-KO mice (7±2 vs 10±2 nmol/10g/min). With LPS, muscle phe flux changed from net release to net uptake in all groups ($P<0.05$, LPS vs Control).
Conclusion: stimulated muscle protein synthesis in early endotoxemia is mediated by NOS.

Low plasma arginine concentrations in tumour-bearing mice are not compensated by increased de novo arginine production in the kidney

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Cancer cachexia is mainly characterized by increased muscle protein breakdown. This probably serves to mobilize amino acids, especially arginine (arg), to support the acute phase reaction in the liver. In these circumstances, arg is important for cell mediated immunity and cytokine production. The reduced plasma arginine concentration we previously observed in tumour-bearing mice could therefore be unfavorable in cancer. Besides protein breakdown, de novo arginine production from citrulline (cit) uptake in the kidney is an important source for endogenous arg production. This pathway could be up regulated by increasing cit production from glutamine (gln) in the gut. Therefore, we studied whether renal arg production is increased in tumour-bearing mice.
In anesthetized mice bearing a subcutaneous tumour (T) and controls without a tumour (C), blood was sampled from the carotid artery and renal, hepatic and portal vein. Blood flow was measured using a radioactive PAH dilution technique. Amino acid concentrations were determined by HPLC. Net balances were calculated as: nb = plasma flow x [arterial]-[venous]. Significance was tested using t-test.
Plasma arg concentrations were reduced in tumour-bearing mice (T: 77±10 μM vs C: 114±5). Gut plasma flow and gut net gln uptake were increased in T ($p<0.05$ vs C). Gut net cit production in T was 23±6 and in C 8±1 nmol/10g bw/min ($p<0.05$). Liver net cit uptake was increased in T (19±6 vs 1±2 nmol/10g bw/min in C; $p<0.05$). Renal net cit uptake was decreased in T (10±3 vs 17±2 nmol/10g bw/min in C; $p<0.05$) and renal net arg production was not significantly changed (T: 11±4 and C: 17±3 nmol/10g bw/min).
Conclusion: In mice bearing a tumour, low plasma arg concentration increased gut cit production, but did not result in increased de novo renal arg production, probably because of increased liver net cit uptake. Thus, the increased need for arg in cancer is not compensated for by an increased renal de novo arg production.

Mannan-binding Lectin Plasma Levels in the Acute Phase Response Following Major Abdominal Surgery: a 'Not So Acute' Phase Protein

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Low plasma levels of the acute phase protein (APP) Mannan Binding Lectin (MBL) have been associated with infectious disease, in particular in secondary immunodeficient conditions. The APPs C-reactive protein (CRP) and secretory Phospholipase A2 (sPLA2), have a joint function in activating the classical route of complement after binding to microorganisms and necrotic cells. MBL may have analogous functions. The role and kinetics of MBL in the post-operative acute phase response following major abdominal surgery and its interplay with CRP and sPLA2 are the subjects of this study.
Clinical outcomes, infectious parameters and APPs (sampling: preop, days 1-10 and 6 weeks postop) were assessed in 20 consecutive patients undergoing transhiatal esophagectomy, with 10 healthy controls as reference standard. Patients were classified as low (n=10) and high-level (n=10) MBL producers by their preoperative levels using a cut-off level of 0.5 ug/ml, which correlates with infectious complications and genetic mutations.
MBL-levels rose less and more gradually than CRP and sPLA2 (peak: MBL day 10: 4x (±0.6); CRP day 3: 85x (±21); sPLA2 day 1: 65x (±22)). Kinetics of CRP resembled those of sPLA2; MBL kinetics opposed them. plasma MBL levels were significantly reduced in low-level producers at all times ($p<.001$). Relative increase: High-level producers: significantly raised from day 5 - 6 weeks compared to preop levels ($p=.005$). Low-level producers: limited rise, only reaching significance on day 7 & 10 ($p=.02$). Maximal increase: 9.5x (>3x higher than previously reported). Comparing the groups: No differences in infectious parameters and complications; Kinetics of the APPs were strikingly different.
MBL plays a subsidiary role in immunocompetent patients following major surgery and its infectious complications. MBL-levels influence CRP and sPLA2 levels, suggesting shared and complementary functions. The 0.5 ug/ml level identifies individuals who cannot produce MBL in high amounts.

Gene expression in the human small intestine. Mediating effects of iron-induced lipid peroxidation

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Iron induces lipid peroxidation and the subsequent release of antioxidants in the lumen of the small intestine. This may mediate gene expression in the intestinal wall. The present study aimed to determine which genes are mediated by an iron-induced oxidative challenge in the human small intestine.
Ten volunteers (22+/-2 y) were tested on two separate occasions. After an overnight fast, duodenal biopsies, taken in the horizontal part of the duodenum, 15 cm distally from the pylorus, were obtained by duodenoscopy. Subsequently, a catheter was inserted into the proximal small intestine with an injection port positioned in the proximal descending duodenum. After positioning, saline was injected at 10 ml/min and, after reaching steady state, either 80 or 400 mg iron as ferrous gluconate was injected for 30 min. Finally, saline was perfused for another 60 min. A second duodenoscopy was performed to obtain tissue samples after the iron challenges. In the tissue samples, gene expression was measured using Affimetrix U133A microarray chips (> 20.000 known genes).
A total number of 9880 genes were expressed in the small intestine. The expression of 91 genes was significantly changed by both the low and the high iron perfusion, whereas 293 genes tended to be regulated by the two iron challenges. Twenty-eight genes were statistically upregulated, whereas 63 genes were significantly downregulated by the two iron interventions. Two of the upregulated genes serve functions in cell growth and tumor suppression, one gene encodes for selenoprotein P, which has antioxidant properties. Interestingly, two genes downregulated by iron are also associated with tumour suppression and negative control of cell proliferation.
Conclusion A large number of genes is expressed in the human proximal small intestine. Iron administration, resulting in lipid peroxidation, mediates expression of at least 91 genes in the small bowel.

Normal 24 hours pattern of gastric and jejunal PCO2 in 10 healthy volunteers

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It has been shown that patients with symptomatic chronic mesenteric ischemia (CMI) show increased postprandial PCO2 measured by tonometry. Slow and time-consuming measurement technique hampered further use of this technique in the past. With recent introduction of automated measurements and data storage 24 hours testing can be performed, which may increase the diagnostic value. To establish the normal pattern, and there from threshold values, we performed gastric and jejunal PCO2 (PG and PJ respectively) during a 24 hours period, each with three different, standardized, meals. In 10 healthy volunteers (HV) gastric pH and gastric and jejunal tonometry catheters were placed. Continuous acid suppression was administered intravenously, using omeprazole (80 mg bolus, followed by 8 mg/hour). The standardized meals, breakfast, diner and a liquid meal (Nutridrink), were given at regular intervals. PG and PJ measurements were automatically performed and recorded every 10 minutes on a computer based program. Threshold values were calculated from 'mean + 2SD'. All HV, with exception of 1, tolerated the 24 hours period well. Overall acid suppression was excellent with pH > 4 in 93.1% (SD 2.7) of time. The fasting PG was 7.1 (SD 1.8), the fasting PJ was 8.3 (SD 1.8), leading to threshold values of 10,7 and 11,9 kPa, respectively. In PG and PJ, Nutridrink gave low peaks. With Nutridrink, the threshold postprandial peak was 10.3 kPa in the stomach and 10.5 kPa in the small bowel.
Conclusions: 24 hours gastric- and jejunal tonometry can be performed easily and accurately. Normal patterns and threshold value in fasting and postprandial periods were established and can be used in diagnosis of chronic mesenteric ischemia.

First results of 24 hours gastric and jejunal PCO2 measurement in the diagnosis of chronic mesenteric ischemia

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In patients with chronic mesenteric ischemia (CMI) an increased postprandial PCO2 measured by tonometry was diagnostic. Slow and cumbersome measurement technique and varying effects of different meals counter acted further use of this technique and have led to development of the tonometry exercise test. With the semi-automated Tonocap and a PC-based program 24 hour (hr) gastric and jejunal tonometry can be easily performed. Normal fasting and postprandial values were established in a healthy volunteer (HV) study. Using these criteria, we evaluated the potential value in patients with clinically proven CMI. We retrospectively analyzed the 24 hr test in patients with subsequently proven CMI. All tonometries were standardized, using intravenously acid suppression and standard meals breakfast (B), diner (D) and a liquid meal (L; Nutridrink), at regular intervals. Gastric pH, gastric (PG) and jejunal (PJ) PCO2 measurements were automatically performed and recorded. Postprandial threshold values from the HV study were calculated from 'mean + 2SD'. Nine patients fulfilled the criteria, mean age 63 (range 26-80) years, 2 males/7 females. Five patients had stenosis of both the celiac artery (CA) and superior mesenteric artery and 4 had isolated CA stenosis. Acid suppression was adequate: pH > 4 in 91,4% (SD 3,4) of time. Overall an abnormal value in any of the postprandial periods was seen in all patients. Gastric values were abnormal in 7/9 and jejunal values in 5/7 patients. No differences were found comparing 1-vessel and 2-vessel disease patients. Comparison of meals shows that L results in 100% abnormal values in both PG and PJ. CMI patients have significantly higher peaks after B and L, compared to HV.
Conclusions: Retrospective results suggest that 24 hr gastric- and jejunal PCO2 measurements can be used to diagnose chronic mesenteric ischemia, using threshold values from a HV study. Prospective studies are necessary to establish the specific diagnostic performance.

The lactose digestive capacity in children with small intestinal mucosal damage: Relation between the new 13C/2H-glucose test and the lactase activity measured in SBB specimens *

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Background: Lactase activity (LA) in a small intestinal bowel biopsy (SBB) specimen is frequently used as indicator for hypolactasia, but its relation with the intestinal lactose digestive capacity has not been established. We compared LA with the results of a new quantitative lactose digestion test, using 13C-lactose as substrate and 2H-glucose as reference.
Method: The results of our Lactose Digestion Test in 18 children aged 0.8 – 18 yr (mean 3.9, SD 2.4) suspected of small bowel mucosal injury were compared to those of the lactose H2 breath test, the histological changes and LA in their SBB specimens. The Lactose Digestion Index (LDI), the ratio of the serum concentration rise of 13C-glucose and 2H-glucose at a representative time period, represents the percentage of the consumed lactose dose, which has been digested.
Results: In 5/6 patients with a normal histology a normal LA was shown, in 1/6 the LA was low. In all 6 the LDI was > 45% and the H2 breath test was normal. In 3 of 5 patients with minor histological changes LA and LDI were both normal, with a normal H2 test. One patient with medium histological changes had a low LA with a normal LDI and a normal H2 result. In 6 patients with severe mucosal damage LA was low in 5/6, but 3/5 demonstrated a normal LDI while the H2 test was normal in 3/6. One patient with severe mucosal damage showed a normal LA with a negative H2 breath test and a low LDI.
Interpretation: LDI shows that the total lactose digestive capacity in patients with mucosal damage can remain adequate, despite low LA in a SBB. Extrapolation of results of single or only a few SBB specimens to the overall lactose digestive capacity has therefore to be considered with caution. This is especially of relevance for the prescription of dietary measurements, as it is known that lactose restriction can have a negative effect on nutritional status. Adequate measurement of the lactose digestive capacity can tailor the dairy consumption advises.

Hydrogen breath tests and abdominal symptoms: how well do they correlate?

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In patients with diarrhea, abdominal cramping or bloating, a hydrogen (H2) breath test may help to elicit lactose malabsorption. However, a discrepancy between test outcome and GI symptoms is not uncommon. Therefore, we conducted a prospective study to investigate the relationship between H2 breath test outcome and the occurrence of abdominal symptoms in a large group of non-selected patients. Five hundred and twenty-three patients, referred for a GI work up, were included between 1997 and 2001 (330 F, age 44±1 yr). After an overnight fast, patients consumed 50 g lactose dissolved in 300 ml of water. Every 30 min during 4 hours, H2 breath samples were taken and symptoms of abdominal pain, cramping, borborygmi, bloating and flatulence were scored on a 10 point VAS scale (1=none, 10=very severe). Test results were considered positive when breath H2 showed a sustained rise of more than 20 parts per million (ppm). A positive symptom score was defined as an increase in VAS-score of more than 2 points compared to basal. One hundred and forty-four patients (27.5%) had a positive test result, with a maximum H2-level at 150 min of 85±7 ppm compared to 5±5 ppm in the H2-negative group ($p<0.001$). In both groups, scores for all symptoms increased compared to basal from 60 min onwards ($p<0.05$), but the increase was significantly larger in H2-positive patients ($p<0.01$). Overall, a rise in breath H2 correlated significantly with an increase in abdominal bloating ($r=0.29$), pain ($r=0.22$), cramping ($r=0.33$), borborygmi ($r=0.34$) and flatulence ($r=0.39$) ($p<0.001$). However, of 144 H2-positive patients, only 81 (56%) had a positive symptom score. Of 180 patients with positive symptom scores, only 81 (45%) had a positive H2 test.
Conclusion: In GI practice, 28% of patients undergoing a H2 lactose breath test has a positive test outcome. In general, GI symptoms correlate significantly with H2 excretion. However, in individual cases, test outcome and symptoms show very poor correlation.

Survival of the probiotic L. plantarum 299V in the gastro-intestinal tract with and without gastric acid inhibition

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Probiotics are emerging as a treatment modality in various gastrointestinal diseases. A placebo-controlled double-blind study was performed to study the effect of gastric acid inhibition on the survival of L. plantarum 299V in the gastrointestinal tract.
Thirty-two healthy volunteers were given pantoprazole (40 mg/day) or placebo during three weeks from day 1 until day 21. In addition, from day 7 until day 21, L. plantarum 299V in an oatmeal fermented drink (10^9CFU/ml) was given twice daily to both groups. From each healthy volunteer, faecal samples were collected at four instances: days 0, 7, 21 and 49 (4 weeks after cessation of L. plantarum 299V and pantoprazole/placebo). Total colony forming units (CFU) per gram faeces of all aerobically and anaerobically growing bacteria were counted as well as the CFU/g faeces of enterobacteriaceae, enterococci, Bacteroides spp., clostridia, bifidobacteria and lacto-bacilli were determined using selective agar plates inoculated with a spiral plater.
Thirty volunteers completed the study (15 in the pantoprazole and 15 in the placebo group). Between day 7 and day 21, median lacto-bacilli counts significantly increased in a similar way from 4.5 (± 0.2 SEM) to 8.1 (± 0.2) log cfu/g faeces ($p<0.05$) in the pantoprazole and from 5.0 (± 0.5) to 7.8 (± 0.2) in the placebo group ($p<0.05$). On day 49 a significant decrease of lactobacilli had occurred in both groups ($p<0.05$). No significant differences were observed in all other bacterial counts between the pantoprazole and placebo group or within the groups during the 49 days study period.
Conclusions: The comparable increases of faecal lactobacilli counts in both the pantoprazole and the placebo treated group demonstrat-es that L. plantarum 299V survives passage through the gastro-intestinal tract irrespective of gastric acidity. The increment of faecal lactobacilli did not seem to modulate the indigenous bowel flora.

Adenocarcinomas of the gastric cardia versus the esophagus: a comparative study with respect to cyclooxygenase-2 expression

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Adenocarcinomas of the gastric cardia and distal esophagus are often considered one clinical entity based on their comparable increasing incidence, prognosis and optimal treatment options. However, it is still a matter of debate if these malignancies have the same etiology and genotype. In a previous study, we demonstrated that induction of the cyclooxygenase-2 (COX-2) protein is an independent prognostic factor in a Barrett carcinoma. The aim of this study was to analyze the role of COX-2 in the development of cardia carcinomas, to correlate the COX-2 expression to clinicopathological parameters and survival, and to compare these findings to the COX-2 results found in esophageal adenocarcinomas.
Tumor sections of 134 patients undergoing potentially curative surgery for an adenocarcinoma arising from the cardia and substantially invading the distal esophagus were immunohistochemically stained using a COX-2 monoclonal antibody. The specimens were blindly scored based on the intensity and extent of COX-2 immunopositivity. COX-2 expression was negative to weak in 59% (COX-2 Low) and moderate to strong in 41% (COX-2 High) of the tumors. This was significantly different when compared to the Barrett carcinomas ($p<0.0001$). COX-2 expression was not significantly correlated with any clinicopathological parameter. Neither could any correlation be found between elevated COX-2 expression and survival. Futher-more, it was noted that in cardia carcinomas the strongest COX-2 expression is seen in the invading margin of the tumor, which was in contrast to the predominantly luminal expression of COX-2 seen in Barrett carcinomas. These results suggest that both malignancies are different entities.
In conclusion, there is a difference in COX-2 expression with respect to intensity, localization, and prognostic significance between adenocarcinomas of the cardia and distal esophagus. This is suggestive for a different etiology and different genetic constitution of these two cancers.

Is high dose rate brachytherapy an alternative to stent placement in the palliation of malignant dysphagia? - A randomized trial

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Both high dose rate (HDR) brachytherapy and metal stent placement are presently used for the palliation of dysphagia in patients with inoperable esophagogastric carcinoma, but their relative merits have not been compared in a randomized trial.
Between December 1999 and June 2002, 209 patients with dysphagia from inoperable esophagogastric carcinomas were randomized to placement of a covered Ultraflex stent (n=108) or single dose (12 Gy) HDR brachytherapy (n=101). Patients were followed prospectively by monthly home visits from a specialized nurse who collected outcome data using standard questionnaires.
Dysphagia improved more rapidly after stenting than after brachytherapy, however after 4 weeks the degree of improvement was similar (p=0.36). Brachytherapy initially failed in 18% of the patients, who then received a stent. Major complications (mainly bleeding, perforation and fistulas) were more common after stenting (25%) than after brachytherapy (13%) (p=0.02), as was the occurrence of recurrent dysphagia from tumor recurrence, stent migration or food-bolus obstruction (40% vs. 29%, respectively) (p=0.02). There was a trend towards more minor complications (mainly mild pain and gastroesophageal reflux) after stent placement (15% vs. brachytherapy: 8%; p=0.08). Median survival was similar for both treatment groups (stent: 145 vs. brachytherapy: 155 days). No major differences in quality of life scores between both treatment groups were observed during follow-up. Total costs, including hospital stay, retreatment and extramural health care, were similar at €9.600 for stenting and €10.400 for brachytherapy. Conclusions: Despite a less rapid relief of dysphagia and a higher initial failure rate, HDR brachytherapy was found to be an attractive alternative to stent placement in the palliation of malignant dysphagia, as brachytherapy was safer with fewer procedures needed for recurrent dysphagia.

European Multicentre Study on Celiac Disease and Non-Hodgkin Lymphoma *

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Background: Previous studies, mostly performed in referral centers, have shown that celiac disease (CD) is associated with an increased risk for malignancies, especially for non-Hodgkin lymphomas (NHL). There is little information about whether clinically silent CD contributes significantly to the burden of NHL in the general population. If this were the case, patients with NHL should have an increased frequency of CD.
Aim: To investigate the frequency of CD, both clinically overt and found by screening, in patients with NHL in controls in Europe.
Methods: A prospective, multi-center, stratified case-control study performed by 12 working groups in 10 European countries. Between May 1998 and April 2001 collected consecutive cases of newly diagnosed NHL were collected. Previously diagnosed CD and silent CD, found after screening by determination of IgA antiendomysial antibodies in serum, was assessed in the same way in the cases with NHL as in the controls.
Results: CD was assessed in 1446 patients with NHL (46%) and in 9659 controls, and it was found in 17 patients (in 4 after screening) and in 49 controls (38 after screening). The patients with NHL had a significantly increased odds ratio (OR) of 2.6 (95% C.I. 1.4-4.9) for CD in comparison to the controls. The increased frequency of CD was due to clinically overt disease as the frequency of disease detected by screening was not increased in the patients with NHL

(OR 1.3; 95% C.I. 0.6-2.7). Among the gastrointestinal lymphomas, the odds for CD were estimated as 28 times higher in those with small bowel lymphoma than in those with other localizations.
Conclusion: In the European population patients with NHL have an increased risk of CD, but the association seems to be lower than previously presumed. CD is mostly associated with T-cell small bowel lymphoma, but this is in general a rare condition. In addition, clinically silent CD found by screening is rare in patients with NHL.

Hyperplastic polyps and hereditary nonpolyposis colorectal cancer

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Hereditary nonpolyposis colorectal cancer (HNPCC) is a genetic syndrome caused by germline mutations in DNA mismatch repair (MMR) genes, in particular hMLH1, hMSH2 and hMSH6. Dysfunction of MMR genes leads to loss of MMR protein expression and to microsatellite instability (MSI). Most cancers in HNPCC patients and almost all MSI(+) sporadic cancers arise in the proximal colon. Hyperplastic polyps (HPs) have been regarded for a long time as benign lesions, lacking potential for neoplastic progression. However, this view is becoming increasingly difficult to sustain and HPs have been proposed to serve as precursor for MSI(+) sporadic colorectal cancers. The aim of this study was to examine whether hyperplastic polyps are also possible premalignant lesions in HNPCC. All hyperplastic polyps resected from patients carrying a mismatch repair gene mutation and/or fulfilling the Amsterdam criteria were retrieved from our screening database. Clinical information concerning age at colonoscopy and location of HPs was collected. MLH1, MSH2, and MSH6 protein expression was evaluated using immunohistochemistry. To verify the correlation between MMR protein expression and proliferation HPs were stained with Mib-1. 86 HPs were resected from 19 male and 18 female HNPCC patients. The mean age at resection was 45.8 years (45.2 years in male and 46.2 years in female patients). Seven (8%) HP were resected from the ascending colon, 8 (9%) from the transverse colon, 1 (1%) from the descending colon, 22 (26%) from the sigmoid and 48 (56%) from the rectum. None of the hyperplastic polyps demonstrated loss of MMR protein expression. Expression of all three MMR proteins overlapped with Mib-1 expression.
Conclusion: Mismatch repair dysfunction in hyperplastic polyps of HNPCC patients is apparently very rare and if found it should be considered a mere coincidence and not a key step in the carcinogenic pathway in HNPCC.

Immunohistochemical expression (IHC) and microsatellite instability (MSI) analysis in families with clustering of colorectal cancer

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Hereditary non-polyposis colorectal cancer (HNPCC) is caused by germline mutations in DNA-MMR genes. Due to the heterogeneity of the mutation spectrum of these genes, screening for mutations is both time-consuming and expensive. Immunohistochemical (IHC) and microsatellite instability (MSI) analysis can be used as pre-screening methods to identify patients with a possible MMR defect. In 1997 international criteria (the Bethesda Criteria) have been proposed that can be used to select families for the determination of MSI. The aims of our study were: 1) to assess the yield of MSI-analysis and IHC-staining in families that meet the various Bethesda criteria and 2) to assess the additional value of PMS2-staining.
Clinical data and tumours were collected from 517 individuals from families with clustering of colorectal cancer (CRC). The pedigrees were numbered according to the Bethesda criteria. MSI-analysis was performed using the five markers recommended by the 1997 workshop. IHC-staining was performed according to standard procedures for hMLH1, hMSH2, hMSH6 en PMS2.
262 pedigrees scored Bethesda positive. A MSI-high/low phenotype in CRC tumors was observed in 21-50% of families that meet the various Bethesda criteria. In families with three relatives with colorectal cancer diagnosed at age >50 yrs, a MSI-high/low phenotype was observed in 14% of the patients. IHC-staining was conform the MSI-results in 85% of the cases. PMS2-analysis was performed in 192 tumours. In 10.9% it gave addittional value to the hMLH1 results. MSI- and IHC-analysis are both good methods to use in Bethesda positive families for CRC subjects. The value of hMLH1-staining is greatly improved in combination with PMS2-staining. We recommend to perform MSI-analysis as first step in families that meet the Bethesda criteria (excluding the Amsterdam criteria). In families that meet the Amsterdam criteria, we recommend to perform IHC as first step in order to direct analysis of the gene involved.

Tumor phenotype and genetic expression are not correlated with clinical behavior in rectal carcinoma after radiotherapy

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In rectal carcinoma, two major tumor types (adenocarcinoma and mucinous carcinoma) can be distinguished based on morphology and on the genetic pathways along which these tumors develop. Data from our previous studies suggest that despite these genetic differences some mucinous carcinomas may be derived from adenocarcinomas.
To evaluate this possibility both types of tumors were analysed, using clinical, histological, RNA and protein analyses. In the setting of a large randomised clinical trial (n = 1449) we obtained a series of carcinomas that showed a phenotype switch from normal adenocarcinoma towards mucinous carcinoma after short-term radiotherapy. This subgroup was analysed together with non-irradiated and irradiated adenocarcinomas and mucinous carcinomas.
The radiotherapy-induced mucinous carcinomas share clinical factors with the adenocarcinomas from which they are derived, and are different from mucinous carcinomas which phenotype they share. The relevance of the subdivision of the mucinous carcinomas into induced and pre-existing was tested by using the follow up data of the clinical trial and showed a remarkable good prognosis for the induced mucinous carcinomas (91.2% versus 39.3% recurrence free survival, p = 0.02). The expression profile of the induced mucinous carcinomas was very closely related to that of their uninduced counterparts, especially with regard to the mucin genes. Immunostaining for various proteins important in the development of mucinous carcinoma was not different between the various tumors.
We showed that gene expression in rectal tumors is related with morphologic tumor features rather than prognosis.

In primary care IBS patients, concurrent anxiety and/or depression is associated with impaired Health Related Quality of Life (HRQoL)

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Secondary care IBS patients have a low HRQoL, possibly because of concurrent mood disorders. Primary care IBS patients are reported to have less mood disorders and a better HRQoL. We have previously found high prevalence of mood disorders in primary care IBS patients. We aimed to determine whether in Family Practice mood disorders negatively influence the HRQoL of IBS patients.
412 Consecutive adult patients from 33 family practices were enrolled in an epidemiological study. HRQoL was assessed using the Short Form 36 (SF-36) which has 8 subscales; physical functioning (PF), role limitations due to physical problems (RP) and to emotional problems (RE), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), and general mental health (MH). SF-36 subscales go from 0 (worst) to 100 (optimal health). Presence of mood disorders was assessed by the Hospital Anxiety and Depression Scale (HADS). Total scores on the 8 subscales of the SF-36 and the two scales of the HADS were calculated.
Complete questionnaires were obtained from all 412 patients. Pairwise comparisons were made between the means, with Bonferroni correction for the p-value. In the group (n=195) without anxiety or depression (A-D-) mean scores of the subscales were 82.1 (PF), 68.9 (RP), 58.1 (BP), 65.6 (GH), 63.4 (VT), 80.7 (SF), 86.5 (RE), and 78.5 (MH). In the group (n=119) with anxiety only (A+D-), mean scores dropped significantly (*$p<0.001$) compared to the A-D- group in 5 out of 8 subscales to 78.5 (PF), 58.4 (RP), 53.2 (BP), 55.6* (GH), 51.4* (VT), 67.9* (SF), 69.1* (RE), and 61.8* (MH). In every subscale, scores significantly ($p<0.001$) dropped in the group (n=89) with anxiety and depression (A+D+) compared to the A-D- group to 70.3 (PF), 28.4 (RP), 46.3 (BP), 42.3 (GH), 34.8 (VT), 26.1 (SF), 42.3 (RE), and 42.3 (MH).
In a primary care IBS population HRQoL is low. Concurrent anxiety and/or depression has a significantly negative effect on the patients' HRQoL.

Desmoid tumours in patients with Familial Adenomatous Polyposis

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Desmoid tumours (DT's) are slow-growing tumours that consist of proliferations of well-differentiated fibroblasts. The prevalence of a DT in patients with Familial Adenomatous Polyposis (FAP) is 7-12%. Initiation by trauma has been described as one of the risk factors of a DT.
We studied the risk of a DT in the Dutch FAP families with a family history of at least one DT.
The Dutch FAP family registry was used. DT's occurred in 39 patients of 28 families. In these families we calculated the overall risk of a DT as well as the risk of DT's in family members of DT patients. Also, we compared the lifetime risk of a DT after colectomy with ileo-rectal anastomosis (IRA) and colectomy with ileo pouch anal anastomosis (IPAA) as well as the risk of a DT if colectomy was performed at age < 25 years, compared to >25 years.
The average age at diagnosis of a DT in 39 patients (21 males) was 34 (3-54) years. Six of 39 patients had more than one DT. Location of the tumour was: intra-abdominal (28), abdominal wall (3), extra-abdominal (1), combined (6), and unknown (1). The overall lifetime risk of a DT in the 28 families was 38% and 12% in family members of patient with a DT. The risk of a DT after IPAA was higher than after IRA. There was no difference in the risk of a DT between patients operated <25 and >25 years. Surgery failed or was impossible in 5 out of 10 patients that needed secondary surgery after IRA because of rectal adenomas.
The risk of a desmoid tumour in families with at least one desmoid lies between 12 en 38 percent. The risk of a desmoid tumour appears to be higher after IPAA. Secondary surgery after IRA in patients with a desmoid is often complicated or even impossible.

Volume measurements of the anal sphincter complex using 3D transanal ultrasonography

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The aim of this study was to determine the volume of the anal sphincters and the anal pressure profile in healthy subjects using 3D transanal ultrasonography (TU) and vector manometry.
Thirty healthy subjects were recruited (mean age 33.4, range 18-61 years), 10 men, 20 women (10 non-parous en 10 parous women). A questionnaire was used to assess bowel habits. Volume measurements were performed by determining the sum of the area of the internal sphincter (IAS), external sphincter (EAS) and puborectalis (PR) measured at 0.25 mm intervals using 3D TU. The anterior, posterior and mean length of the anal canal were determined on TU. Resting anal pressure, maximal squeeze pressure and length of the anal sphincter were assessed during manometry. The results were compared using the Kruskall Wallis Test (median, p-value).
All subjects had a Vaizey score of 0. The IAS and EAS volumes were significantly higher in men (1.4 cm^3 vs. 0.9 cm^3 and 0.8 cm^3, p=0.017 and 6.6 cm^3 vs. 4.6 cm^3 and 4.6 cm^3, p=0.053). There were no significant differences in PR volume between men and women. The anterior, posterior and mean sphincter length were significantly larger in men (2.2 cm vs. 1.4 cm and 1.2 cm, p=0.001, 3.2 cm vs. 2.8 cm and 2.4 cm, p=0.012 and 2.6 cm vs. 2.1 and 1.8, p<0.001). While no significant differences were found in resting anal pressure, maximum squeeze pressure was significantly higher in men (242 mmHg vs. 163 mmHg and 155 mmHg, p=0.025). The sphincter length measured during manometry was also significantly larger in men (3.8 cm vs. 2.6 cm and 2.6 cm, p=0.001).
Conclusions: 3D TU adequately assesses EAS and IAS volumes. These volumes and sphincter lengths are greater in men than in women. Parity did not influence these results. The manometry results showed a higher maximum squeeze pressure and a larger sphincter length in men. These results will now be compared with results in fecal-incontinent patients in order to assess the clinical value of volume measurements.

COX-2 expression and molecular alterations in Peutz-Jeghers hamartomas and carcinoma

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Peutz-Jeghers syndrome (PJS) is a hamartomatous polyposis disorder with a high cancer risk. Debate exists about the pre-malignant potential of hamartomas. Also, treatment options are not available other than surveillance. Therefore, molecular alterations in hamartomas and PJS carcinomas were studied. The aim was (i) to evaluate expression of COX2 as target for chemopreventive treatment and (ii) to define the neoplastic potential of hamartomas at the molecular level. 24 PJS hamartomas, including 2 hamartomas with dysplastic changes, and 11 PJS carcinomas were available. Slides were stained with antibodies against COX-2, ß-catenin, cyclinD1, p21waf1, Ki67, and p53. DNA was studied for LOH at 19p (STK11), 5q (APC), and 17p (p53); mutations in ß-catenin, APC and K-RAS; and MSI. Epithelial COX-2 was present in 25% of hamartomas, including two hamartomas with dysplastic changes, and 64% of carcinomas. Several hamartomas showed focal nuclear ß-catenin (17%) and cyclinD1 overexpression (29%), unrelated to dysplasia at re-examination. Disturbed topographical expression of Ki67 in relation to p21waf1 was focally present in 27% of hamartomas, including those with dysplastic changes. Most carcinomas showed nuclear ß-catenin (71%), cyclinD1 overexpression (71%) and aberrant Ki67 staining (100%). There was LOH at 19p in 32% of hamartomas and 82% of carcinomas. p53 staining was present in 4 (36%) carcinomas, one of which showed 17p LOH. No ß-catenin mutations were found. APC mutations were present in 2 carcinomas, but LOH at 5q was not found. Two carcinomas had K-RAS mutations, one carcinoma had MSI.
Conclusions: COX-2 expression in PJS carcinomas and dysplastic hamartomas provides a rationale for chemoprevention with NSAIDs or COX-2 inhibitors. Focal immunohistochemical changes, which may indicate a pre-malignant potential, were present in some non-dysplastic PJS hamartomas. Molecular changes in PJS related tumors are distinct from the usual adenoma-carcinoma sequences.

What is the added value of corpus biopsies to antral biopsies for the determination of H. pylori status?

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One or more biopsies are taken from the stomach to determine H. pylori status. However, it is unclear in how many instances H. pylori containing mucosa may not be sampled if only antral or only corpus biopsies are collected. The aim of the present study is to determine the added value of corpus biopsies to antral biopsies for the determination of H. pylori status. Furthermore, we will assess the association between H. pylori present only in the corpus and patient characteristics.
The study group consisted of patients who underwent an upper gastrointestinal endoscopy at a single center between January 1995 and May 1997. Antral and corpus biopsies were taken at each endoscopy for determining H. pylori status: 2 antral and 2 corpus biopsies for histological examination and 1 antral and 1 corpus biopsy for CLO-test.
A total of 620 patients underwent upper gastrointestinal endoscopy. In 80% of the endoscopies there was total agreement between the performed biopsy tests. Histology of the corpus was the only negative test in 6%. The addition of corpus biopsies increased the diagnostic yield by 31/307 (10%, 95% CI 6.6-13%), in H. pylori-positive patients. These patients more often showed atrophy and intestinal metaplasia as compared to other test outcomes for H. pylori status in antrum and corpus, 37% versus 20%, respectively (OR 2.2, 95% CI 1.1-4.4).
In conclusion, taking both antral and corpus biopsies would seem to be preferable to antral biopsies for assessment of H. pylori status. Patients having H. pylori only in the corpus showed significantly more often atrophy and intestinal metaplasia.

Local ablation methods in unresectable hepatic metastases of carcinoid tumours

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Hepatic metastases of carcinoid tumours cause incapacitating symptoms of diarrhoea and flushes. Local treatment by hepatic artery embolisation (HAE) has shown a response of 38% to 57%. Radiofrequency ablation (RFA) has also been described in the therapy of carcinoid metastases. In this paper we describe our experiences with local ablation techniques in the management of carcinoid patients with hepatic metastases and failing systemic treatment.
Fifteen consecutive carcinoid patients (11 men and 4 women; median age 60 years; range 45-71 years) with liver metastases were treated with either HAE with Ivalon particles or RFA (percutaneously or intra-operatively) between January 2000 and May 2002. Follow-up for evaluation was performed by CT-scan and 24-hours urine 5-HIAA excretions.
In total 17 HAE's were performed in 13 patients and 10 lesions in 3 patients were treated with RFA. Median duration of symptoms was 19 months. Median overall decrease of 5-HIAA excretion 2 months after HAE was 32% with tumour regression on CT-scan in 4 patients (30%) and improvement of symptoms with a median duration of 15 months in 3 of them (23%). Postembolisation syndrome (elevated liver function tests and fever) occurred in 5 patients, one patient developed a liver abscess and another transient hepatic failure. No toxic deaths were reported. The 3 patients treated with RFA showed a biochemical response of 34, 81 and 93% respectively, with tumour regression in all of them. Improvement of symptoms was reported in 2 patients up to 25 months. One patient suffered from transient cholestasis after RFA.
Conclusions: Liver embolisation performed late in the clinical course had limited effect on symptoms and biochemical and radiological parameters. First experiences with RFA are favourable and might encourage to apply RFA in an earlier stage of metastatic carcinoid.

Blastocystis hominis: commensal or pathogen?
A double-blind, placebo-controlled study in children with recurrent abdominal pain *

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There is no consensus about the pathogenicity of Blastocystis hominis, an anaerobe protozoan mainly inhabiting the caecum and colon. In 72 children presenting with recurrent abdominal pain (RAP) and B. hominis in their stools other causes for RAP were excluded by means of a physical examination and laboratory investigations. These included a full blood count with leucocyte differentiation, C-reactive protein, liver and renal function tests, amylase, IgA, anti-endomyseal antibodies, Helicobacter pylori serology, urine analysis and stool cultures. When indicated an EEG, abdominal X-ray, lactose or glucose hydrogen breath test was performed. In 26 children another cause for the RAP was found and in 19 RAP dis-appeared spontaneously. The remaining 27 children, with persisting RAP and normal laboratory tests at follow-up, were asked to participate in a randomized, double-blind, placebo-controlled trial. The children in the intervention group were treated with metro-nidazol 50 mg/kg/day for 10 days and those in the control group received placebo. After randomisation 13 children received metro-nidazol and 14 placebo. After treatment 31% of the children in the intervention group had positive stools compared to 79% of the placebo group (P=0,016). There was however no difference in the frequency of RAP between the groups, 62% versus 57% (P=0.563). Although the number of children included in the trial is small, it appears, that B. hominis does not cause RAP.

Are drugs an underestimated (co)factor in the etiology of acute pancreatitis?

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Drugs are considered a relatively rare cause of acute pancreatitis. The true incidence of drug-associated pancreatitis (DAP) is not known.
From January 1997 until October 2002, 60 patients with acute pancreatitis where admitted to our hospital. Risk factors including all drugs used at the time of admission, disease course and outcome were evaluated retrospectively. The following criteria were used to classify the probability of causality: definite: at least three reported cases in the literature of a recurrent pancreatitis attack after re-challenge; probable: at least one reported case of a recurrent pancreatitis after re-challenge; possible: multiple case reports but no re-challenge.
16 out of 60 patients (27%) used drugs reported to be associated with acute pancreatitis. Five patients used drugs classified as definitely causally related (azathioprine N=1, azathioprine + prednison N=1, mesalazine N=1, didanosine N=1, alpha calcidol N=1). The patient using azathioprine and prednison developed a recurrent attack after re-challenge with azathioprine.
Seven patients used a drug classified as probable causally related (hydrochlortiazide N=3, hydrochlorthiazide + simvastatin N=1, simvastatin + ACE inhibitor N=2, simvastatin N=1).
Four patients used a drug classified as possibly causally related (ACE inhibitor N=2, chlorthalidon N=1, ciclosporin N=1). Six patients (10%) had no other risk factors besides medication. Four 6 (10%) patients had other risk factors/diagnosis (biliary pancreatitis N=5, peritoneal dialysis N=1)
Conclusions: A surprisingly high percentage of patients (27%) used medication reported to be associated with DAP when admitted because of an attack of acute pancreatitis. Ten percent of patients had no other risk factor besides medication. In cases with concomitant risk factors drugs may act as a co-factor or disease modifier.

Induction of rat hepatic and intestinal UDP-glucuronosyltransferases by naturally occurring dietary anticarcinogen

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Gastrointestinal tumours are among the most common malignancies in Western society, the majority of which is associated with dietary and lifestyle factors. However, dietary compounds have also been able to reduce gastrointestinal cancer rates both in humans and animals. Though the exact mechanism leading to the anticarcinogenic action of these compounds is not fully known, it has been demonstrated that this chemopreventive capacity may be due to elevation of the glutathione S-transferase detoxification enzymes. Now we investigated the effect of several anticarcinogens on the gastrointestinal UDP-glucuronosyltransferase (UGT) enzymes. Diets of male Wistar rats were supplemented with ellagic acid, ferulic acid, Brussels sprouts, quercetin, α-angelicalactone, tannic acid, coumarin, fumaric acid, curcumin and flavone separately, and combinations of α-angelicalactone and flavone. Hepatic and intestinal (proximal-, mid-, distal small intestine and colon) UGT enzyme activities were quantified by using 4-nitrophenol and 4-methylumbelliferone as substrates. All anticarcinogens tested increased UGT enzyme activity with both substrates, at least at one of the five different sites investigated. α-Angelicalactone, coumarin and curcumin showed enhanced UGT enzyme activities at all five sites. Both small and large intestinal UGT enzyme activities were increased by quercetin, α-angelicalactone, coumarin, curcumin and flavone. Except for tannic acid, all agents induced hepatic UGT enzyme activity. Furthermore, dietary administration of α-angelicalactone and flavone, given individually or in combination, even at relatively low concentrations, enhanced the UGT detoxification system in the liver and to a lesser extent in intestine. In conclusion, induction of gastrointestinal UGT enzyme activities after consumption of dietary anticarcinogens, may contribute to a better detoxification of potentially carcinogenic compounds and subsequently to the prevention of gastrointestinal cancer.

Sitosterolemia in ABCG5-null mice is aggravated upon activation of the liver X-receptor LXR

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Mutations in either ABC-half-transporters G5 or G8 cause sitosterolemia, an inborn error of sterol metabolism characterized by strongly elevated plasma concentrations of plant sterols. ABCG5 and ABCG8 have been proposed to heterodimerize into a functional complex that mediates the secretion of plant sterols and cholesterol by hepatocytes into bile and their efflux from enterocytes into the intestinal lumen, thus limiting accumulation in the body. To test whether deficiency of ABCG5 alone is sufficient to induce sitosterolemia in mice, ABCG5-null mice were generated. ABCG5-deficiency was associated with elevated plasma levels of beta-sitosterol (37-fold) and campesterol (7-fold) and reduced plasma cholesterol concentrations (-40%). Plant sterols amounted up to 40% of total sterol content in the liver in knock-out mice. Retention of orally administered 3H-sitosterol in the intestinal wall (+ 550%) and plasma (+640%) was markedly higher in ABCG5-null mice. Surprisingly, high plasma beta-sitosterol and campesterol concentrations were further elevated in ABCG5-null mice upon treatment with the synthetic LXR agonist T0901317, whereas this treatment resulted in a reduction of plasma plant sterol concentrations by ~75% in wild-type mice. Cholesterol content of gallbladder bile was similar in ABCG5-null mice and controls and equally increased in both strains upon LXR activation. Hepatic expression of ABCG8 was reduced by about 35% in ABCG5-deficient mice when compared to controls and induced to a similar extent in both strains upon LXR activation. No compensatory overexpression of other ABC transporters potentially involved in hepatic cholesterol trafficking was observed. Our data show that disruption of the ABCG5 gene alone is sufficient to cause hyperabsorption of dietary plant sterols and sitosterolemia in mice whereas biliary sterol secretion is not affected. These findings may indicate distinct physiological roles for ABCG5 and ABCG8 in intestine and liver.

Reduction of normothermic ischemia and reperfusion (I/R) injury of the liver after administration of interleukin-10 (IL-10)

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Liver ischemia and reperfusion (I/R) injury is a major contributor to posthepatectomy liver failure following extensive liver resections. This type of injury is characterised by liver cell necrosis during ischemia followed by an inflammatory response after reperfusion resulting in increased parenchymal and microvascular damage. It has been shown that IL-10 is a potent anti-inflammatory cytokine. In this study, the effect of exogenous, recombinant IL-10 was investigated in a rat model of *in situ* liver I/R.
Male Wistar rats were used (300-400g). Liver ischemia was induced by clamping of the vessels to the median and left-lateral lobes rendering 70% of the liver ischemic for 60 minutes. Recombinant rat IL-10 (rrIL-10) was administered iv (50 µg/kg) prior or post ischemia. The rats were randomly allocated to 5 groups: group 1 (I/R without rrIL-10, n=6), group 2 (I/R with rrIL-10, pre-ischemia, n=6), group 3 (I/R with rrIL-10, post-ischemia, n=6), group 4 (I/R with anti-rat IL-10 neutralising antibody, pre-ischemia, n=6) and group 5 (SHAM, rrIL-10 without I/R, n=6). AST and IL-6 were assessed prior to ischemia and 30 minutes, 6 and 24 hours after ischemia. After 24 hours of reperfusion bile production was measured after which the rats were sacrificed.
The AST values were significantly elevated in groups 1-4 compared to group 5 up to 24 hours after ischemia ($p<0.02$). After 6 of reperfusion AST (U/L) was significantly elevated in group 1 compared to group 2 (4128±742 / 2188±405 resp. (mean±SEM) $p<0.05$). IL-6 was significantly elevated after 30 minutes and 6 hours of reperfusion in group 1 compared to the other groups ($p<0.05$). Bile production was significantly elevated in groups 2 and 5 compared to group 1 (4,8±0,2 and 4,9±0,3 vs. 3,8±0,2 (µL/min/100g) $p<0.02$).
Conclusions: rrIL-10 administration prior to liver ischemia reduces parenchymal damage to the liver and preserves liver function in the rat. Anti rat IL-10 neutralising antibody appears to neutralise IL-6.

Cystic fibrosis mice have an impaired capacity to dilute their bile, leading to increased cytotoxicity

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Aim: Cystic Fibrosis related liver disease is characterized by bile duct damage and biliary fibrosis. We hypothesize that cytotoxicity of bile is increased in cystic fibrosis(CF), for example due to impaired capacity of cholangiocytes to dilute bile. We studied bile formation in Cftr-/- and control mice under basal conditions and after feeding a bile salt(BS) enriched diet for 3 weeks.
Methods: Cftr-/- mice and Cftr+/+ littermates (controls) were fed standard lab chow or a diet supplemented with 0.5%(wt/wt) cholate for 3 weeks, after which bile was collected for 20-30 min by gallbladder cannulation. Bile flow rate, and biliary BS and phospholipids(PL) concentrations were determined. Results are given as mean ±SD (n=4-6 per group).
Results: Under basal conditions, bile production did not significantly differ between Cftr-/- and control mice with respect to flow rate (5.4±1.2 vs. 5.4±1.2 µl/min.100g), BS concentration (46±22 vs. 45±33mM) or BS secretion rate (0.3±0.1 vs. 0.3±0.2 µmol/min.100g; resp.). After the cholate supplemented diet, however, bile flow rate was lower in Cftr-/- mice, compared with controls (13.7±3.0 vs. 17.9±1.7 µl/min/100g; resp., $p<0.01$), despite similar biliary BS secretion rates (1.3±0.3 vs. 1.0±0.2 µmol/min/100g; resp., NS). Under this condition, biliary BS concentration was 40% higher in Cftr-/- mice (98±22mM), compared with controls (58±12mM, $p<0.01$). Since biliary PL concentrations were similar in Cftr-/- and control mice on the BS diet, PL-to-BS ratio was 41% lower in the former (0.10±0.02vs. 0.17±0.06; resp., $p<0.05$). Liver histology was similar in Cftr-/- and control mice after the BS diet.
Conclusion: During dietary BS supplementation, Cftr-/- mice produce bile with increased BS concentration and a decreased PL-to-BS ratio, compared with controls. Since a decreased PL-to-BS ratio has been implied in cytotoxicity and bile duct damage, we hypothesize that an impaired capacity to dilute bile contributes to CF related liver disease.

Cyclosporin A inhibits bile salt synthesis rate and increases plasma triglycerides after liver transplantation in children

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Cyclosporin A (CsA) is widely used after orthotopic liver transplantation (OLT) and is associated with hyperlipidemia. We discontinue CsA treatment several years after pediatric OLT, provided that there are no signs of cholestasis or rejection (liver biopsy). This regimen allows to determine whether CsA affects synthesis rate of bile salts, as has been demonstrated in rats, or is associated with disturbances in lipid metabolism.
To assess the effects of CsA on synthesis rate and pool size of the primary bile salts cholate (C) and chenodeoxycholate (CDC) and on plasma lipid levels in children after OLT.
Before and after discontinuation of CsA in pediatric OLT patients, pool size and synthesis rate of C and CDC were measured using a stable isotope dilution technique, and related to plasma lipids. To test the null hypothesis (no effect of CsA discontinuation) we used as test statistic the number of patients whose all measurements without CsA exceeded those with CsA. Exact one-sided P-values of this test are presented.
In 6 children (age: 3-16.4 years; 4M/2F) CsA treatment was discontinued at a mean of 3.5 years (sd: 2.5 y) after OLT (biliary atresia n = 5; choledochal cyst, n=1). Discontinuation of CsA increased synthesis rate of CDC (+38%, $p<0.001$) and tended to increase that of C (+25%, $p=0.05$). Discontinuation of CsA increased the pool size of CDC (+ 54%, $p<0.001$), but not that of C. Discontinuation of CsA decreased plasma levels of cholesterol (-7 %, NS) and triglycerides (-22%, $p<0.01$). Plasma triglyceride levels appeared inversely correlated with synthesis rate of CDC ($r = -0.64$, $p<0.05$).
Conclusions: In pediatric OLT patients, suppression of bile salt synthesis by long-term CsA treatment may contribute to hyperlipidemia and thus to increased risk for cardiovascular disease.

Improving the balance between apoptosis and regeneration in acute liver failure (Final report MLDS project WS 99-28)

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Apoptotic cell death of hepatocytes occurs in many liver disease and contributes to liver failure in these diseases. The mechanisms of apoptotic cell death are diverse: cytokines, in particular TNF, oxidative stress and bile acids can all induce apoptosis of hepatocytes. Improvement of the anti-apoptotic potential of hepatocytes may attenuate cell loss and liver failure in liver diseases.

Aim: to elucidate the mechanisms of apoptosis of hepatocytes caused by TNF, bile acids and oxidative stress. To develop strategies to improve the anti-apoptoic potential of hepatocytes. Hepatocytes were exposed to the apoptotic stimuli TNF, the apoptotic bile acid glycochenodeoxycholic acid and oxidative stress (menadione, a superoxide anion donor). The importance of intracellular survival pathways in the resistance against apoptosis was investigated by blocking these pathways at specific points. Potential anti-apoptotic agents were tested in this setting.

Results: the transcription factor NF-kB is essential in the protection against TNF-induced apoptosis, but against oxidative stress and bile acid induced apoptosis. This indicates the importance of NF-kB regulated anti-apoptotic genes. Inducible nitric oxide synthase (iNOS) and Inhibitor of apoptosis-2 (cIAP2; a caspase inhibitor) were identified as NF-kB regulated protective proteins. Both NO, the product of iNOS and overexpression of cIAP2 protected against TNF-induced apoptosis. The effectiveness of cIAP2 is now tested in an in vivo model of acute liver failure. The therapeutically used bile acid tauroursodeoxycholic acid (TUDCA) protected against GCDCA induced apoptosis, but not against TNF or oxidative stress induced apoptosis. The protective effect of TUDCA is dependent on the activation of survival pathways p38 MAP kinase and PI-3-Kinase. Overexpression of cIAP2 protected against GCDCA-induced apoptosis.

Finally, oxidative stress induced apoptosis was inhibited by the iNOS product NO and the superoxide dismutase mimetic MnTBAP, but not by TUDCA. Inhibition of caspase-8 and the adaptor protein FADD prevent apoptosis induced by TNF but not by GCDCA and oxidative stress.

Conclusion: TNF, oxidative stress and bile acids induce apoptosis via different mechanisms. The NF-kB regulated genes iNOS and cIAP2 are promising candidates to prevent apoptosis in general. In addition, TUDCA is a promising anti-apoptotic agent to prevent bile acid induced apoptosis.

Impaired antigen presentation capacity and IFN-α production by dendritic cell populations of chronic hepatitis B patient

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Resolution of a hepatitis B (HBV) infection is characterized by a vigorous, multispecific T cell response. Dendritic cells (DC) play an important role in the induction of a virus-specific T cell response. Some individuals fail to clear the virus and become chronically infected. It has been suggested that the function of dendritic cells of patients with chronic viral hepatitis is impaired. To further characterize these defects two major precursor subsets of DC were isolated from the peripheral blood of chronic HBV patients (n=8) with high viral load (HBV-DNA>10^5 geq/ml) and elevated ALT levels or healthy controls (n=5) using magnetic cell sorting techniques with specific antibodies. Myeloid DC (mDC) were isolated with an anti-CD1c (BDCA1) antibody after depletion of $CD19^+$ cells from the peripheral blood mononucleair cells. Plasmacytoid DC (pDC) were isolated with an anti-BDCA4 antibody. No differences in percentages of mDC (lineage$^-$,$CD1c^+$ (BDCA1), $CD11c^+$, $CD123^{low}$) and pDC (lineage$^-$, $BDCA4^+$, $CD11c^-$, $CD123^{high}$) between chronic HBV patients and healthy controls were observed. The antigen presenting capacity of DC types were studied in an allogenic mixed leucocyte reaction, i.e. DC cultured with T cells from a healthy volunteer. The allostimulatory capacity of mDC but not of pDC was decreased in patients with chronic HBV. pDC represent the major source of endogenous IFN-α, a key cytokine involved in the antiviral response. A significant decreased IFN-α production by pDC was found in response to stimulation with Staphylococcus aureus Cowen 1 antigen (SAC) in chronic HBV patients (523 ± 290 pg/ml versus 1888 ± 230 pg/ml in healthy controls, p=0.01). The current findings indicate that continued HBV replication in chronic patients might be due to a defect in antigen presenting capacity of mDC and IFN-α production of pDC. Further research should determine the mechanisms by which the virus is able to suppress the DC functions.

Gallstones, gallbladder and gastrointestinal motility in β-thalassemia major (BTM) adults in southern Italy

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Multiple gastrointestinal dysmotility – e.g hypomotile gallbladder - is found in pts. with cholesterol gallstones and, to a lesser extent, in pigment stone pts. β-thalassaemia major (BTM) is a genetically determined condition with high prevalence of pigment gallstones, chronic hemolysis & hyperbilirubinemia. We studied 23 adult normoglycaemic BTM patients (M:F=7:16; age 25.6±SE0.8 yrs; periodical blood transfusions + oral deferoxamine) for gallbladder content + motility (sonography), and upper and lower intestinal tract dynamics (i.e. gastric emptying: sonography; orocecal transit time, OCTT: H_2-BT; colonic function: diary + Bristol Stool Form). Potential implications of deferoxamine-induced autonomic nervous system (ANS) dysfunction on motility were assessed by Sweat-spot-test + 8 cardiovascular tests. Controls were 108 healthy subjects.
Results: Solitary stones (9-16 mm) or sludge in a thin-walled gallbladder were found in 30% and 27% of pts., respectively, with none ever experiencing colicky pain. Compared to controls, BTM patients had increased gallbladder fasting (38.0±4.8 mL vs. 21.7±0.6 mL, P<0.0005) and postprandial residual (7.9±1.3 mL vs. 5.5±0.6 mL, P< 0.004) volumes, despite preserved contraction. After 8-12 mo. follow-up, a persistently “small” (<27mL) fasting gallbladder remained stone/sludge-free. Where as BTM patients had normal gastric emptying and weekly bowel movements, OCTT was longer than controls (132.0±7.8 min vs. 98.3±1.9 min, P<0.0001). ANS dysfunction was found in 62% of pts, irrespectively of stone/sludge formation and motility indices. Conclusions: adult BTM patients have high prevalence of asymptomatic gallstone/sludge, preserved gastric emptying and delayed small intestinal transit, not associated with ANS dysfunction. Formation of gallstones and sludge appears to be promoted when fasting gallbladder volume increases with time. This study provides further insights into mechanisms of gallstone pathogenesis in BTM.

Inflammatory bowel disease after liver transplantation: the effect of immunosuppressive regimens

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Background: The use of different immunosuppressive regimens might be responsible for the conflicting reports on the prevalence and severity of inflammatory bowel disease (IBD) after liver transplantation.
Aims: To study retrospectively the prevalence and severity of IBD after liver transplantation in patients on different maintenance immunosuppressive regimens. Patients: All 78 patients with end-stage primary sclerosing cholangitis (48 patients) or auto-immune cirrhosis (30 patients), transplanted between 1979 and July 2001, and with a follow-up of at least one year. Methods: Besides patient and transplant characteristics, data on IBD and immunosuppression before and after transplantation were collected. The Kaplan-Meier method was used for IBD free survival analysis. Possible risk factors for IBD after transplantation were analysed by Cox univariate and multivariate regression. Results: Follow-up after transplantation was median 7.2 years (1.1-22.3). Nine of 25 patients with pretransplant IBD experienced flare-ups at median 1 year (0.3-4.6) after transplantation. Six of 53 patients without pretransplant IBD developed de novo IBD at median 3.9 years (1.1-6.3) after transplan-tation. The cumulative risk (standard error) for IBD was 6 (3), 12 (4), and 20 (5)% at 1, 3, and 5 years after transplantation, respectively. The 5 years IBD free survival was significantly higher in patients without tacrolimus 90(4)% versus tacrolimus 36(17)%, in patients with azathioprine 88(4)% versus without azathioprine 54(13)%, and in patients on the regimen prednisolone-azathioprine-cyclosporine A 89(5)% versus tacrolimus-prednisolone 58 (16)%. Pretransplant IBD and the use of tacrolimus were found to be independent predictors for IBD after transplantation.
Conclusions: The prevalence and severity of IBD after liver transplantation is affected by the immunosuppression used. Azathioprine seems to have a protective, and tacrolimus a promoting effect.

Liver preservation by hypothermic, pulsatile continuous perfusion using a new colloid-based perfusion solution

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Recent literature has shown promising results in preserving livers by hypothermic machine perfusion (MP). The standard solution for MP is the UW-G solution (modified University of Wisconsin). In our search for a next generation MP preservation solution we have developed Polysol. This colloid based perfusion medium contains free radical scavengers, buffers and is enriched with specific nutrients for the liver. We hypothesize that Polysol results in higher quality preservation after 24 hours of hypothermic MP than the standard UW-G solution.
In an isolated rat liver perfusion model hepatocellular damage was assessed during reperfusion after 24 hours hypothermic MP in UW-G (n=4) or Polysol (n=5). To determine liver parenchymal damage AST, ALT and LDH were measured at 10 minute intervals, during 60 minutes of normothermic reperfusion with oxygenated Krebs-Henseleit Buffer. Control livers were reperfused after 24 hours cold (static) storage in UW-CS (n=5) or were directly reperfused after explantation (n=5).
MP with UW-G showed lower levels of damage parameters when compared to livers stored statically with UW-CS for 24 hours: ALTt=40: 8.25± 1.65 vs 26.80± 2.29 ($p< 0.02$) and LDHt=40: 99.75± 28.5 vs 237±13.36 ($p< 0.02$). Livers machine perfused with Polysol also showed lower levels of damage parameters when compared to livers cold stored for 24 hours (UW-CS): ALTt=40: 3.2 ± 0.92 vs 26.8± 2.29 ($p= 0.0079$) and LDH t=40: 53.60± 8.88 vs 237.8± 13.36 ($p= 0.0079$). Livers machine perfused with Polysol however showed better preservation at all time points when compared to livers perfused with UW-G: ALT t=40: 3.2± 0.92 vs 8.5± 1.71 ($p< 0.05$), LDH t=40: 49.66± 11.32 vs 99.75± 28.50. Overall there were no significant differences in perfusate flow (ml/min) (28.91± 1.06 vs 31.96± 0.98).
Conclusions: MP with UW-G or Polysol results in better quality liver preservation than cold, static storage with UW. MP of rat livers in Polysol is superior to machine perfusion in UW-G.

Hepatitis C Virus (HCV)-specific immunity after Extracorporeal Whole Body Hyperthermia in patients with chronic HCV infection

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Besides the use of extracorporeal whole body hyperthermia (EWBH) as a treatment for several forms of malignancies, EWBH has shown to induce an antiviral effect in HIV/HCV coinfected patients. Since this effect might start weeks after the procedure, it is assumed that HCV specific T-cell immunity is (one of) the effector mechanism(s).
A single application of EWBH (body core temperature raised to 41.8^{o} +/- 0.15^{o} for 2 hrs, Temet ^{TM}, First Circle Medical, Minneapolis, USA) was performed in 13 patients with HCV genotype 1 and non-response to previous therapy, to study the safety, early effects and immunity pattern. All 13 patients have been followed for 24 weeks. Blood samples were collected pre-treatment, at day 1, weeks 1, 2, 3, 4, 8, 12, 16, 20 and 24.
General and HCV specific immunity was studied by measuring serum cytokines and T-cell proliferation to HCV- and recall antigens. Moreover, HCV-specific T-cells were quantified and characterized by immunofluorescent detection after stimulation of PBMCs with different HCV peptides restricted to HLA-A2 or -B7. The cells were stained for cell surface markers (CD4, CD8, CD69) and intracellular cytokines (ICC: IL-2, IFN-γ, TNF-α).
The serum cytokines TNF-α, IL-1β, IL-6 and IL-10 increased during the procedure in all patients. Also, 4 to 20 weeks after the EWBH a second increase was seen. The T-cell proliferation to HCV antigens significantly increased in 10/13 patients with an optimum 2 to 6 weeks after the EWBH. The ICC results show that preferently CD8 positive T-cells are activated in response to the stimulation. Little IFN-γ is produced, whereas some IL-2 production was detected in CD4 and CD8 T-cells. Strongest was the TNF-α response to nearly all HCV peptides in both CD4 and CD8 T-cells.
In conclusion: a strong general and HCV specific response is induced after EWBH in chronic hepatitis C patients non-responding to former therapy. This might be a clue for developing new treatment modalities.

Viral dynamics during tenofovir therapy in patients with lamivudine-resistant hepatitis B mutants

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The occurrence of YMDD drug resistance mutants (DR-mutants) during lamivudine therapy leads to Hepatitis B Virus DNA (HBV DNA) breakthrough. Tenofovir, a new nucleotide analogue reverse transcriptase inhibitor, appears to be effective against YMDD DR-mutant population. We investigated the additional effect of tenofovir on the viral kinetics of the hepatitis B virus after HBV DNA breakthrough during lamivudine therapy.
Seven chronic HBV patients with breakthrough HBV DNA on lamivudine therapy received tenofovir (300mg od). Four of these patients were HIV co-infected. YMDD variants were detected using a line probe assay (INNO-LIPA HBV DR; Innogenetics N.V., Ghent, Belgium) Sequential sera, taken at day 1; t=0 and t=8 hours, day 2, 4, 7, 10, 14, 21 and day 28, were tested for HBV DNA by quantitative and qualitative PCR. The decay of the viral load followed a bi-phasic decline and was fitted by a bi-phasic-exponential model according to Neumann.
All patients were male, median age 36 year (range 26-53 years, n=7); six patients were HBeAg-positive at baseline. Analysis of the YMDD motif of the HBV polymerase gene at breakthrough showed a methionine-to-valine substitution; rtM204V (YVDD variant), in all patients (n=7).Viral kinetic data of the first 5 patients will be described hereafter. Median baseline HBV DNA was 1.46 x 109 geq/ml (range 3.0x10 6- 5.75 x 10 9) Application of tenofovir resulted in a mean log HBV DNA decline of 2.2 +/- 0.99 (n=5). The median effectiveness of blocking viral replication was 93% (range 87%-98%). Turnover of free virus was 18.9 hours (median; range 14.9-69.3 hours), the turnover of infected hepatocytes was estimate to be 7.3 days (medium; range 3.7-17.9 days).
In conclusion: Tenofovir is capable of blocking viral replication in patients with lamivudine induced mutant viruses. These first viral kinetics data of tenofovir show an efficacy capable of inactivate disease, but insufficient to eliminate viral replication completely.

Pretreatment Intrahepatic CD8+ Cell Number Correlates with Virological Response to Antiviral Therapy in Chronic Hepatitis

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Interferon-ribavirin therapy is successful in only half of the chronically infected hepatitis C patients. The role of pretreatment presence and localization of immune factors on subsequent res-ponse to therapy is incompletely defined. Therefore, we analyzed in an exploratory study the relationship between response (undetec-table HCV RNA in serum) and baseline immune factors such as 1) intrahepatic CD4, CD8 and CD68 expression, 2) peripheral immune parameters such as plasma IL-10, IL-12, IFN-γ levels and 3) peripheral HCV-specific T-cell reactivity in a consecutive series of 17 chronically infected patients who completed 26 weeks of interferon-ribavirin therapy within a RCT.
Intrahepatic CD8 positive cells located in the portal tracts of pretreatment liver biopsies were found to be significantly higher in patients responding to therapy (n=9) than in non-responders (n=8) (p=0.002). The relation between portal CD8 positive cells and chance of response could be described by a logistic curve (univariate logistic regression analysis); its prognostic value was superior to that derived from genotype and other baseline factors (multivariate analysis). In contrast, peripheral cytokine levels nor HCV specific T cell reactivity in peripheral PBMCs did show a relationship to therapy response. These findings suggest that significant prognostic immune markers are to be found in the liver, and should encourage further study of hepatic immune cells as important predictive factors.

Mars treatment in posthepatectomy liver failure

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Posthepatectomy liver failure (PHLF) is a dramatic complication following extensive liver resection or liver resection in a compromised liver. In spite of improved peri- and postoperative patient management and intensive care treatment, PHLF has a mortality of 80 – 100%. The failing remnant liver with increasing toxin levels in these patients is not able to regenerate. Molecular Adsorbent Recirculating System (MARS) is a liver support device capable of extracting water and protein bound toxins out of the blood in liver failure patients. Clearing toxins by MARS treatment may result in overcoming PHLF in patients who have undergone major liver resection. Experience in the Netherlands, so far, includes five patients with progressive PHLF treated with MARS in three hospitals. Patient one underwent five MARS treatments lasting six hours per treatment; patient 2, three treatments ranging from five to eleven hours; patient 3, 10 treatments ranging from 6 to 24 hours; patient 4 and 5 underwent three and five treatments respectively lasting 8 hours each. In all patients, improvement of biochemical parameters (plasma ammonia, bilirubin, lactate, urea and creatinin) was observed during MARS treatment. In patient 3 for example, plasma total bilirubin concentration decreased from 625 to 250 mM and ammonia concentration decreased from 220 to 160 mM after the first MARS treatment. In three patients clinical improvement was observed in terms of hemodynamic stabilization, improvement of neurological condition (coma scale), and improvement of renal function. One patient (patient 1) survived. After initial clinical improvement in two patients (patient 3 and 5), sepsis severely complicated the clinical course and these patients finally died due to this complication. In conclusion, application of MARS in PHLF patients showed marked biochemical and clinical improvement in the course of 3-10 treatments. Its contribution to ultimate outcome of PHLF remains to be established.

Doctor to patient transmission of hepatitis B: the problem and new solution

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The problem: Health care workers (HCW) who perform exposure-prone procedures, pose a small risk for transmitting hepatitis B (HBV) to patients. From 1974-1996 289 cases of doctor-patient transmission of HBV have been described in 13 publications. The risk of doctor to patient blood contact during major surgery is 3%. Transmission of hepatitis B mainly occurs when levels of viremia exceed 10^7 copies/ml(cpm). Public health measures focus on excluding HCWs with viremia > 10^5 cpm from performing exposure prone procedures, irrespective of skills or documented transmission.
The solution: From 1997 onwards we monitored 11 HCWs periodically for levels of HBVDNA and started antiviral therapy when levels were repeatedly above 10^5 cpm. Antiviral therapy initially consisted of lamivudine monotherapy, but in recent years lamivudine in combination with interferon, entecavir or tenofovir have been used. The number of days that viremia was below 10^7 cpm and 10^5 cpm respectively was calculated; transition from one level to another was assumed to occur at halfway. In 5 HCWs with HBeAg-negative chronic hepatitis B the percentage days per year with viremia > 10^5 cpm fell from 31% in 1997 to 8% in 2001; the percentage days > 10^7 cpm decreased from 23% to 0. In 6 HBeAg-positive HCWs the percentage days with viremia > 10^5 cpm remained stable around 56%, and that of > 10^7 cpm about 41%. In 2002 1 HBeAg-positive HCW with lamivudine resistant viremia > 10^9 cpm started entecavir, that reduced viremia below 10^5 cpm.
Conclusions: The approach to convert high viremia in HCW's to low levels thought to be incapable of transmitting HBV in the clinical setting is feasible and has now shown to be effective for HBeAg-negative HCWs. For HBeAg-positive HCWs new drugs like entecavir, adefovir or tenofovir will in all likelihood help to solve the problem.

Double needle biopsy of liver tumours; a new, safe and reliable technique

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In case of a liver tumour, lab tests and radiological imaging can almost always make the diagnosis. In some cases a biopsy is necessary to obtain the diagnosis. A disadvantage is the risk of bleeding and of needle tract metastasis. The latter has received more attention lately and is reported to be around 5%.
In our hospital a new technique was developed where the tumour was punctured using the Double Needle technique with a low risk of bleeding and needle tract metastasis. Using this technique, a hollow Menghini needle with a needle inside is inserted under ultrasonic guidance till just before the tumour. After that, a true cut needle replaces the inner needle and the biopsy is performed through this tract. At the end of the biopsiy, the true cut needle can be removed and 1-2 ml of Tissucol can be injected through the hollow needle during which the hollow needle can be removed.
From 1993-1999, 304 biopsies of liver tumours of unknown origin were taken using this technique. In 278 (92%) cases, a diagnosis was obtained: 118 patients (39%) had liver metastasis of a tumour elsewhere, 84 patients (29%) had a benign tumour, 19 patients (6%) had a hepatocellular carcinoma without cirrhosis, 30 patients (10%) had a hepatocellular carcinoma with cirrhosis, 21 patients (7%) had a cholangiocarcinoma, 5 patients (1%) a lymphoma, and 1 patient a hemangioendothelioma. In 26 patients (8 %), no diagnosis could be made: In 6 patients (2%) the tumour could not be visualised, in 20 patients (6%) normal liver tissue was found at pathology. In case of operation, all biopsies were confirmed.
There were 9 complications: 7 patients had a haematoma, 1 patient a biliary peritonitis and 1 patient had a collapse.
There was no procedure related mortality. Until now, no needle tract metastases are observed.
Conclusion: Double needle biopsy is a new, safe and reliable way of puncture of liver tumours. Unnecessary needle tract metastasis and bleeding seem to be prevented.

High-fat enteral nutrition specifically decreases TNF-α and preserves gut barrier function in rats early after hemorrhagic shock

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Endotoxin plays a central role in the pathogenesis of sepsis after severe hemorrhage. Translocation of endotoxin has been proposed to trigger production of inflammatory cytokines (TNF-α) causing gut barrier failure. Previously we showed that high-fat enteral nutrition decreases bacterial translocation 24 hours after hemorrhage. However, it is unknown which mechanisms underlie this protection. Therefore, we investigated the effect of high-fat enteral nutrition on endotoxemia, TNF-α and gut barrier function early after hemorrhage. Rats were subjected to a non-lethal hemorrhagic shock by withdrawing 2.1 ml blood/100 gram b.w. Hemorrhagic shock rats were divided into a group that was starved overnight (HS-S); a group receiving low-fat enteral nutrition (HS-LF) and a group receiving high-fat enteral nutrition (HS-HF). At 90 minutes after shock arterial blood was withdrawn and gut barrier function was assessed ex vivo by measuring horseradish peroxidase (HRP) leakage in an ileum-segment and by determining bacterial translocation to mesenteric lymph nodes (MLN) by culture. Plasma endotoxin in HS-HF rats (3.9 ± 0.6 pg/ml) was significantly lower compared to HS-S rats (15.2 ± 2.2 pg/ml, p=0.001) and HS-LF rats (10.7 ± 0.9 pg/ml, p=0.002). TNF-α levels were lower in HS-HF rats (17.9 ± 10.4 pg/ml) compared to HS-S rats (180.9 ± 67.9 pg/ml, p<0.02) and HS-LF rats (83.5 ± 16.7 pg/ml, P<0.01). HRP leakage was less in HS-HF rats (1.1 ± 0.4 µg/ml) compared to HS-S rats (4.2 ± 1.1 µg/ml, p≤0.05). Also, bacterial translocation to MLN was lower in HS-HF rats (median 5 cfu/gram tissue, range 0-27) compared to HS-S rats (80 cfu/gram, (39-135), p<0.01) and HS-LF rats (41 cfu/gram, (5-103), p<0.01).
This study clearly shows that high-fat enteral nutrition specifically decreases endotoxin and TNF-α in plasma, thereby preserving gut barrier function early after hemorrhage. High-fat enteral nutrition may provide a new therapy in preventing the inflammatory response preceeding sepsis.

The predictive value of intrahepatic CD8 T-lymphocytes and HBV core expression in relation to response to antiviral therapy for chronic hepatitis B patient

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Recognition of HBV-infected hepatocytes by CD8 T-lymphocytes is important for viral clearance. Expression of hepatitis B core antigen (HBcAg) in HBV-infected hepatocytes can trigger this antiviral T-cell response. We investigated the role of intrahepatic CD8 T-lymphocytes and HBcAg expression in relation to response to antiviral therapy.
Forty chronic HBeAg+ patients treated with either lamivudine (n=20;100 mg/day for 11 to 169 weeks) or IFNα (n=20;10 MU tiw sc for 32 weeks) were selected as result of treatment. Ten patients in each treatment group were responders (HBeAg negativity and normalization of ALT). Liver biopsies were performed before and after therapy. CD8 T-lymphocytes and HBcAg expression were detected by an immunocytochemical double stain. CD8 T-lymphocytes and HBcAg+ hepatocytes (nuclear and cytoplasmic expression) were quantified per 10 lobular fields. The number of pretreatment CD8 T-lymphocytes was significantly higher in responders compared to nonresponders (15.5 vs. 9.5;p=0.008). In responders baseline nuclear core expression tended to be lower (4.0 vs. 12.5;p=0.09). Cytoplasmic expression was not significantly different between responders and nonresponders (2.5 vs. 1.5;p=0.46). The number of CD8 T-lymphocytes correlated with cytoplasmic core expression (rs=0.31;p=0.04). Longitudinal analysis showed a significant reduction of CD8 T-lymphocytes after treatment in responders (pre- 15.5 vs. posttreatment 9.0;p<0.001), but not in nonresponders (9.5 vs. 9.0;p=0.70). Multivariate analysis revealed pretreatment CD8 T-lymphocytes and age, but not ALT and HBV DNA, as independent prognostic factors for response (n=40). The number of pretreatment intrahepatic CD8 T-lymphocytes was the only independent prognostic indicator for IFNα (p=0.03); it was of borderline significance for lamivudine therapy (p=0.06).
Conclusion: The number of pretreatment intrahepatic CD8 T-lymphocytes is a novel independent predictor of response to antiviral therapy.

Whole body protein synthesis and breakdown are unchanged after major hepatectomy for malignancies in man

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In the fasted state, the rate of appearance of the essential amino acid phenylalanine (Qphe) is a measure for whole body protein breakdown. Phe is either used for protein synthesis or hydroxylated to tyrosine (Qphe-tyr). Hitherto, it was assumed that Qphe-tyr only took place in the liver but recently it was suggested that there is a role for the kidney as well. Using stable isotopes, Qphe and Qphe-tyr (as a semi-specific liver function) can be measured. From these data protein synthesis can be calculated.
9 patients undergoing laparotomy aiming for major hepatectomy for malignancies in otherwise normal livers were studied. During surgery a 6 h primed continuous i.v. infusion of 2H5-Phe en 2H2-Tyr was administered and arterial blood was sampled hourly. Isotopic enrichment in plasma was measured by LC-MS. Results were related to functional liver volume (FLV) assessed by CT-volumetry and calculated as total liver volume minus tumor volume. 4 Patients were irresectable, 2 patients underwent metastasectomy (<2% FLV resected) these 6 patients served as controls.
Mean (SEM) resected volume in the remaining 3 patients was 62.7(11.8)%. Protein breakdown prior to resection per kg body weight in the total group (n=9) was 39.4(2.0) µmol/kg bw/h. During surgery no significant differences were observed between resected patients and controls. Qphe-tyr before resection in the total group was 3.23(0.27) µmol/kg bw/h and did not change following resection. Consequently, whole body protein synthesis (baseline 36.2(1.92) µmol/kg bw/h) is unchanged by major hepatectomy. Assuming that renal hydroxylation is unaffected by hepatectomy, hepatic Qphe-tyr per gram functional liver tissue increases 2.5 fold after resection ($p<0.005$). Conclusion: Whole body protein breakdown and synthesis are unaffected by major (>60%) resection of normal liver. Following hepatectomy an adaptation occurs keeping whole body phenylalanine hydroxylation unchanged.

Germline mutations in the PRKCSH gene underly autosomal dominant polycystic liver disease

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Polycystic liver disease (PCLD, MIM 174050) is a dominantly inherited condition characterized by the presence of multiple liver cysts of biliary epithelial origin. This condition is distinct from autosomal dominant polycystic liver disease type 1 and 2. Both of these disorders may be complicated by polycystic liver disease, but renal involvement is absent in PCLD. The gene for PCLD has been mapped previously to a 12.5 cM interval on chromosome 19p. We sampled 110 individuals from 4 separate Dutch PCLD pedigrees. Thirthy-two individuals fulfilled the ultrasonographic criteria for PCLD. We carried out fine mapping and established linkage to marker D19S581 ($Z_{max}=9.65$; $p<0.01$) with a maximal multipoint LOD score of 10.96 for the interval between D19S583 and D19S581. The genomic interval contains 78 genes and EST clusters and after screening 677 exons, sequence analysis revealed a splice-acceptor site mutation in intron 15 of the PRKCSH gene in 3 families and a splice-donor site mutation in intron 4 of the PRKCSH gene in 1 family. These mutations segregated completely with the disorder in these families. The splice site mutations cause intron retention and generate premature stop codons, eliminating the C-terminal part of the protein. The protein is predicted to be an endoplasmatic reticulum protein and is named hepatocystin by us.
Conclusion: These findings establish germline mutations in the PRKCSH gene as the cause for PCLD.

The role of endoscopic Doppler ultrasound in patients with peptic ulcer bleeding

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Peptic ulcer bleeding is a common medical emergency with substantial rebleeding and mortality rates. Stigmata of recent hemorrhage are important prognostic signs, but are subjective. We evaluated the potential diagnostic value of Doppler assessments in patients with peptic ulcer bleeding.
A prospective multicenter study was performed among patients with peptic ulcer bleeding. First stigmata of recent hemorrhage (Forrest classification) were classified. Next the ulcer base was assessed by a 16 Mhz endoscopic Doppler ultrasound system (Neurosoft, Sipplingen, Germany). A positive Doppler signal was defined as a reproducible pulsatile flow up to 1 mm of depth. Patients with a Forrest Ib-IIb and positive Doppler ulcer received endoscopic injection therapy. Patients with a Forrest IIc-III and positive Doppler ulcer were randomly allocated for endoscopic therapy or no therapy. None of the ulcers without Doppler signal received endoscopic therapy, independent of the Forrest classification. After endoscopic hemostatic therapy again Doppler assessment was performed.
A total of 80 patients were included, 57 with a positive Doppler signal. From all Forrest Ib-IIb ulcers, 82% had a positive Doppler signal. Of all Forrest IIc-III ulcers, 47% had a positive Doppler signal. There was no difference in rebleeding, surgery or mortality rate between the Forrest Ib-IIb group with and without Doppler signal. Rebleeding did occur in 2/9 patients with Forrest Ib-IIb ulcers without Doppler signal. Clinical outcome in the Forrest IIc-III group with and without Doppler signal was good. There was a trend towards higher rebleeding rate in the group where Doppler investigation, immediately after endoscopic hemostatic therapy, remained positive (3/11 vs 1/27, p=0.06).
Conclusion: This study did not reveal the additional role of endoscopic Doppler assessment when added to the Forrest classification in clinical decision-making in patients with peptic ulcer bleeding.

Digestive and systemic complications following oral ingestion of concentrated acetic acid or alkaline agent

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Ingestion of concentrated (80%) acetic acid (CAA) or alkaline agents (alkali) is a common method to attempt suicide in certain populations. We compared the occurrence of complications and outcome in patients who had ingested CAA or alkali. We also evaluated the value of endoscopy performed within 12-24 hours after ingestion.
Records of 179 patients (85 CAA; 94 alkali) admitted for ingestion of a caustic agent were reviewed and scored for systemic and gastrointestinal complications and outcome. The DiCostanzo classification was used to grade mucosal injury.
Mucosal injury was more severe in the CAA group than in the alkali group (median: grade 2 vs. 1; p=0.013). Hospital stay was longer (mean: 9.9 vs. 7.2 days; p=0.01) and admittance to ICU more frequent (44% vs. 22%; p=0.002) in the CAA group. Systemic complications were more common in the CAA group and included renal and hepatic insufficiency, diffuse intravascular coagulation and hemolysis (24% vs. 3%; p<0,001). Perforations were only seen in the CAA group (6% vs. 0%; p=0.017); there was no difference in the occurrence of strictures (15% vs. 17%). Mortality was higher in the CAA group (14% vs. 2%; p=0.003). More severe mucosal injury at endoscopy was the only predictive factor for the occurrence of systemic and gastrointestinal complications and mortality (RR 9; CI 3 – 30). Treatment of strictures by endoscopic dilation was moderately successful: 34% of all strictures (29 patients, mainly esophageal) could be treated by dilatation alone (n=10), whereas the other patients were primarily (n= 7) or secondarily (n= 11) referred for surgery. One patient with an esophageal stricture died of systemic complications.
Conclusions: CAA ingestion is associated with a high incidence of gastrointestinal and systemic complications and mortality. Early endoscopy is safe and gives important prognostic information. Endoscopic treatment of caustic strictures is only moderately successful.

Video Capsule Endoscopy in Small Bowel Crohn's Disease

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Crohn's disease only in the small bowel occurs in 30-40% of patients, of which 10% have no ileal involvement. The diagnosis can be made on enteroclysis and/or endoscopy with biopsies. Enteroclysis is difficult to use for follow-up, as it is patient unfriendly, has high radiation exposure, is operator-dependent and is unable to detect small lesions. With the introduction of the video capsule endoscopy (VCE), a novel way of small bowel imaging is available, allowing the mucosa of the small bowel to be studied as a video. Aim was to investigate the usefulness of VCE in patients with suspicion of small bowel Crohn's disease.
Patients known with small bowel Crohn's disease were included in this study, when they presented with symptoms compatible with exacerbation, but enteroclysis showed no abnormalities. VCE was performed after an overnight fast in ambulant patients.
Five patients (4 M, 1 F: age 16-48 yrs) were included. One patient had only a few shallow erosions. One patient had symptoms suggesting obstruction, which was not seen on enteroclysis. At VCE, the capsule re-entered the stomach and remained there for hours, allowing only a small part of erosive jejunitis to be visualized. One patient had mainly distal ulcerative jejunitis. One patient had proximal ulcerative jejunitis, with a normal distal jejunum. In one patient VCE showed erosions diffusely throughout the jejunum. In all patients, the capsule was normally excreted. Patients tolerated VCE very well. No adverse events were noticed.
We conclude that VCE is a safe and helpful tool in patients with small bowel Crohn's disease. It may find mucosal abnormalities in the absence of pathology in enteroclysis. Although VCE is expensive and time consuming at analysis, it should be included in the diagnosis and management of selected IBD patients.

Long-term Follow-up of the First Ten Patients Treated with the Gatekeeper Reflux Repair System

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Introduction: The Gatekeeper Reflux Repair System (Medtronic, Minneapolis MN) is an endoscopic anti-reflux therapy in which hydrogel prostheses are implanted in the submucosa of the distal esophagus to augment the lower esophageal sphincter. In a fase-I study, 10 patients using daily PPI medication were treated between 11/2000 and 6/2002 and followed for 6 months. Primary outcome parameters of this study were safety and efficacy. We now report on the long-term follow-up of these patients.
Methods: Originally, 10 patients were included in the pilot-study of which 2 patients had their prostheses removed at 3 wks and 7 months, respectively. This report entails the follow-up of the remaining 8 patients of whom medical charts were reviewed and who were contacted by phone for an oral questionnaire.
Results: One of the 8 patients could not be contacted (lost to follow-up). His last follow-up data was acquired 5 months after completion of the pilot study at which time he was well and not using any medication. 7 pts were contacted by telephone (median follow-up time 21m; range 18-25). 6 out of 7 pts reported a sustained improvement of their reflux symptoms at the time of follow-up. These 6 patients regarded the Gatekeeper procedure a valuable contribution to the control of their symptoms. 1 pt was completely off medication, 2 patients were taking antacids less 3 days/wk, 1 pt was using PPI less than 3 days/wk, and 3 pts were on daily PPI-medication (two pts using a lower dose than before implantation). There were no late adverse events. 2 pts had a follow-up endoscopy 24 months after implantation. In both patients all prostheses were in place and situated in the submucosa at the original site.
Conclusion: Long-term follow-up of the first series of patients treated with the Gatekeeper Reflux Repair System shows that symptom improvement is sustained in the majority of patients while using no or significantly less PPI medication at a median of 21 months post implantation.

MRI is a patient friendly and accurate alternative to ileocolonoscopy in determining disease activity in crohn's disease

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In Crohn's disease (CD) Ileocolonoscopy (IS) is the gold standard for appraisal of localization and severity of mucosal damage, but this procedure is invasive and poorly tolerated. In this study we compared (non-invasive) MRI of the small bowel and colon without duodenal intubation (MRSC) with IS in determining disease activity in CD.
From February to November 2002, 25 CD patients undergoing IS for disease severity assessment were included. During IS location, CD endoscopic index of severity (CDEIS) and overall grading of severity (no, mild, moderate or severe inflammation) were scored. MRSC was performed within 2 weeks before or after IS. Bowel preparation at MRSC consisted of no food ingestion for 4 hours and oral intake of minimal 1 L of water 2 hours prior to scanning. Patient experience at IS and MRSC was determined. All MR-images were blindly analyzed for location and overall grading (no, mild, moderate or severe inflammation). Exact correlation or one level of difference in grade of severity between MRSC and IS were considered appropriate.
Of 25 patients, 6 showed severe, 6 moderate, 5 mild and 8 no activity at IS. In 21 patients there was an exact correlation (n=14) or one level of difference (n=7) in agreement between MRSC and IS. There was a significant correlation between grading at MRSC and IS ($P \leq 0.05$ $r=0.45$), although not between MRSC and CDEIS. In 4 patients discrepancies in degree of disease activity were observed. In 5 patients intubation of the terminal ileum was impossible at IS. At MRSC in 4 of these patients a stenosis of the terminal ileum was seen. The presence of inflammation seen at IS and MRSC correlated in 87 of 117 bowel segments. 5 of 117 segments were found positive at CS but not at MR. 25 of 117 were found positive at MR but not at IS. All patients, except one, preferred MRSC.
Conclusion: MRSC is a feasible, simple, non-invasive technique for disease assessment in CD patients, demonstrating an excellent tolerability and accuracy.

Implications of routine endoscopic brush cytology in suspected biliopancreatic cancer: patient management and cost savings

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Endoscopic brush cytology lacks sensitivity which holds back many gastroenterologists form obtaining it routinely. We assessed the diagnostic accuracy of brush cytology in suspicious common bile duct (CBD) strictures and analysed its clinical implications.
This retrospective series included 95 patients in whom a total of 104 brush cytology specimens of the CBD were obtained at ERCP. Specimens were classified as normal, atypical, suspicious of malignancy or malignant. The former two were regarded as negative and the latter two as positive for malignancy. Finally, 91 brush cytology specimens from 83 patients were included. In these patients a definite diagnosis was possible based on histopathology results from resection specimens, at least twelve month clinical and radiological follow up, or death.
Strictures were malignant in 68 patients (82%). Fifteen patients had benign strictures (18%). There was one false positive specimen. Overall sensitivity was 63%. In general, it is custom to obtain definite cyto- or histological proof in case of irresectability. Based on the assumption that 80% of patients with a pancreatic head or cholangiocarcinoma will have locally advanced or metastatic disease at clinical presentation and given the 63% sensitivity of brush cytology in our series, the majority of patients would be withheld from a subsequent US or CT guided percutaneous cytologic puncture. This should be regarded as a substantial benefit to patient care because such procedures are invasive and cumbersome to patients. Moreover, it saves additional costs which in the Dutch situation amounts to approximately Euro 5000 per 100 patients with irresectable biliopancreatic cancer.
Conclusions: Endoscopic brush cytology is of value in the management of patients with suspected biliopancreatic cancer because it makes additional US or CT guided cytologic punctures redundant in the majority of patients with irresectable disease. This improves patient care and saves costs.

Efficacy of Wallstents in benign biliary strictures due to chronic pancreatitis

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In patients with chronic pancreatitis (CP) 10-30% develop symptomatic biliary strictures. Conventional biliary stenting is often complicated by stent obstruction. Wallstents (WS) have a longer patency but are impossible to remove and therefore not primarily indicated for benign stenosis. However, in selected patients in whom conventional stenting fails and who have a contraindication or refuse surgery, a WS might be considered. Between 1994 and 1999, thirteen patients were treated with placement of a WS for benign biliary obstruction due to CP (mean age 56 years, 5 woman, 8 man) and were evaluated until the end of the follow-up period in November 2002. All patients were previously treated with plastic stents. Etiology was alcohol (n=8), divisum (n=1) and idiopathic (n=4). Success of treatment was defined as adequate biliary drainage by a WS (including placement of a second WS through the first in case of stent dysfunction of the latter). Indication for primary WS placement: contraindication to surgery (n=10), presumed inoperable pancreas carcinoma (n=1), inoperable because of other malignancy (n=1), refused surgery (n=1). Endoscopic WS placement was successful in all patients. Mean follow-up was 50 months (range 6 days-86 months). Early complications occurred in one patient. Nine patients (69%) were successfully treated by a WS: a patent first WS (n=5), a patent second WS inserted through the first WS (n=3) and one patient with a patent WS after cleaning by a balloon. In four patients WS treatment was not successful: a PE stent was inserted through the WS in three and one patient underwent surgery. Mean WS patency (KM) was 60 months (95% CI 43 months-77 months). At 33 months the probability of stent patency was 75%.
Conclusion: Placement of a WS is safe and provides successful and prolonged biliary drainage in a selected group of patients with benign biliary obstruction due to CP in whom surgical intervention is not possible or desirable.

Malignant gastric outlet and duodenla obstruction - results of endoscopic stent insertion

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Obstruction of stomach-duodenum occurs in advanced malignancy. We performed a review of endoscopic gastroduodenal stenting. Between 1996 – 2002 40 patients (31 males, median age 58 years (28-89 years)) underwent palliative stenting. Underlying primaries: stomach (n=17), pancreas (n=9), colon (n=4), others (n=10). Sites of obstruction: stomach (n=16), duodenum (n=25), gastroenterostomy (n=3), multiple (n=4). In 44 sessions we used: uncovered enteral Wall stents (n=27), uncovered Choo stents (n=27) and others (n=5). Stent placement was technically successful 43/44. Twelve patients were treated as outpatients. Median hospitalization after stent placement: 3 days (1-25) in 28 patients. Technical problems with stent delivery: 7x. In total 52/59 stents were successfully deployed. Six pats required 2 and 2 pats 3 stents. A second stent was needed in 3.
Median survival: 52 days (3-498 days). Symptomatic improvement of vomiting in 88%, 63% could tolerate oral nutrition. Feeding tube needed in 11 patients. Worsening of symptoms occurred twice.
Early complications - 8 patients: obstruction treated endoscopically (n=3), cholangitis with percutaneous drainage (n=3) and bleeding (n=2). Late complications - 14 patients: in 4 patients stent fracture, all enteral Choo-stents after a follow-up of 29-393 days. Two were removed at laparotomy, one endoscopically. Five patients needed renewed endoscopic interventions due to stent occlusion. Upper GI-bleeding occurred in 4 patients with a fatal
outcome in 2. Two patients required percutanous drainage because of cholangitis. No complications were seen in 16 patients.
Conclusion: Endoscopic insertion of expandable stents is possible in malignant gastroduodenal obstruction. Obstructive symptoms are relieved in most patients. Both early and/or late complications are related to the stents and advanced stage of the underlying malig-nancy. In one type of stent (Choo-stents) fracture of the Nitinol-wire occurred.

Long-term results of endoscopic drainage for biliary strictures due to chronic pancreatitis

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Background: Endoscopic stent therapy is an established treatment modality to resolve postoperative benign biliary strictures. In analogy, biliary strictures due to chronic pancreatitis (CP) are frequently treated by endoscopic stenting, but results regarding long-term outcome are scarce.
Methods: All CP patients who underwent endoscopic drainage of the common bile duct for a benign stricture in our hospital between 1987-2000, were included in this retrospective study. Patient charts were reviewed and long-term follow-up was obtained by written questionnaires.
Results: 58 CP patients were included (median age 54, 44 male) with alcohol as the predominant cause of pancreatitis (64%). Median duration of drainage was 274 days (range 45-2706), with a median stent exchange of 2 (range 0-17).
Procedure related mortality rate was 2%. This patient died of a cerebral infarction a day after surgical intervention for a duodenal perforation caused by ERCP. Other complications were a liver abscess which was surgically drained and a mild flare-up of pancreatitis.
Median follow-up was 45 months (range 0-182). In 35 patients the stenosis could not be resolved. 5 of these patients remained stent dependent and 30 underwent further treatment (bypass surgery in 18 and insertion of a wall stent in 12). Endoscopic treatment was successful in 22 patients (38%), of which 18 are still alive and none developed a recurrent stenosis after a median follow-up of 85 months. With multivariate analysis no predictors of outcome were identified besides presence of peri-pancreatic infiltration due to concomitant acute pancreatitis. A sub-analysis in these 12 patients revealed a success rate of 92% (11/12), as opposed to only 24% (11/46) in the group without acute inflammation.
Conclusions: For biliary strictures due to CP without evidence of concomitant acute inflammation, long-term success rate of endoscopic therapy is rather poor and only 1 out of every 4 strictures is resolved successfully.

Lack of Association between Toll-Like Receptor 4 Haplotype and Asp299gly Polymorphism and Susceptibility for Inflammatory Bowel Disease

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Toll-like receptor 4 (TLR4) acts as the transducing subunit of the lipopolysaccharide receptor in the detection of Gram-negative pathogens. Recognition of LPS by TLR 4 induces the intracellular signalling pathway that involves activation of NF-κB. In humans the common Asp299Gly mutations results in a blunted response to lipopolysaccharides. Several mutations in NOD2/CARD15 are associated with Crohn's disease (CD) but not in ulcerative colitis (UC). In accordance with TLR4, NOD2 also plays a role in regulating NF-κB activation by interacting with LPS. The aim of this study is to investigate the association between inflammatory bowel disease (IBD) and TLR4. We performed association and transmission distortion analyses with four microsatellite markers around the TLR4 locus. We genotyped 319 patients with CD, 98 patients with UC and 11 patients with indeterminate colitis. Both parents were available for 145 patients, spouse and child for 62 patients, two first degree relatives for 40 patients, one first degree relative for 83 patients; 99 patients participated without any relatives. Allele frequency and genotype distributions of the TLR4 Asp299Gly polymorphism were analyzed in 417 CD patients and 303 controls. Linkage disequilibrium was observed between all pairs of consecutive markers. No difference was found in allele frequency in patients with IBD and the subgroups with CD and UC, as compared with controls. Association analyses of the alleles showed a minimum p-value of 0.35. The Asp299Gly polymorphism displayed no difference in frequency of the alleles between CD patients and controls (13% vs. 15%; p=0.61). Conclusion: The linkage disequilibrium between the tested markers implies that it is expected that preserved haplotypes are present in this region enabling the performance of haplotype analysis. The observed lack of association means that TLR4 appears not to be associated with IBD. The result of the Asp299Gly polymorphism and CD confirms these findings.

IKBL+738 gene polymorfism is associated with high risk for colectomy in Ulcerative Colitis

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The IKBL gene lies telomeric to the TNF-cluster in the central MHC-complex and carries a structural polymorphism at position +738. An earlier report found that severe ulcerative colitis (UC) is associated with IKBL+738C allele in a Spanish population of 155 UC patients. We report the frequency of this polymorphism in a Dutch population of 214 UC patients and in 152 ethnically matched controls. DNA-based techniques previously described were used to type individual alleles of IKBL+738 in the same laboratory in Madrid. Mean follow-up of the Dutch UC population is 9.6 years, 52% of the patients are female. The frequency of the IKBL+738C mutation was 15% in the UC population and 16% in controls. 15 out of 30 patients (50%) with the mutation had extensive disease and 11 (37%) had undergone colectomy. 75 out of 175 patients without the IKBL+738C had extensive disease, 37 (21%) had undergone colectomy.
The IKBL+738C mutation is not related to pancolitis in the Dutch UC population. However, colectomy was more frequent in this patient group. This study supports in part the previous study in Spain and suggests that this gene or a gene in linkage disequilibrium in the short arm of chromosome 6 may be involved in determining a more severe prognosis in ulcerative colitis.

The relevance of the TLR4 Asp299Gly gene polymorphism in the susceptibility to duodenal ulcers and severity of gastric antral inflammation

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Background & Aims: Recent publications suggest that the Toll-like Receptor 4 (TLR4) contributes to intestinal inflammation and imply that alterations in the innate response system may contribute to the pathogenesis of intestinal disorders. We investigated the role of the recently identified functional human TLR4 Asp299Gly gene polymorphism in the susceptibility to duodenal ulcers and the severity of inflammation. Methods: We determined the frequency of the TLR4 Asp299Gly gene polymorphism using a restriction fragment length polymorphism based polymerase chain reaction in Dutch Caucasian patients with endoscopically diagnosed duodenal ulcers (DU n=70) and in healthy controls (HC n=175). The frequencies of the wild-type, heterozygous, and homozygous TLR4 genotypes in the two groups were determined. In addition, histological parameters of inflammation were assessed in antrum biopsy specimens. Results: A two fold increase in the frequency of the TLR4 mutant 2-allele was observed in DU=20.0% versus the healthy controls HC=10.3% (p=0.0575 (OR 2.18 (95% CI: 1.02-4.67)). In patients with the TLR4 Asp299Gly mutation the histological scores of inflammation, activity, and atrophy were higher as compared to patients without this mutation: inflammation 93 vs 74% (p=0.17), activity 57 vs 26% (p=0.062), and atrophy 71 vs 35% (p=0.031).
Conclusions: This study suggests that the functional TLR4 Asp299Gly mutation is involved in DU susceptibility and associated to histological inflammatory abnormalities in the antrum. Since the TLR4 functions as a LPS receptor and duodenal ulcers are strongly associated with Helicobacter pylori (HP) we are in progress of determining the HP status to investigate if the HP status changes our finding on the susceptibility to DU and the severity of gastric inflammation.

In Barrett's esophagus Muc4 and Muc6 can distinguish between high-grade dysplasia and normal columnar epithelium

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Patients with Barrett's esophagus (BE) have a 30-125 times higher risk of developing an esophageal adenocarcinoma. Carcinoma development is a multistep process in which malignant degeneration is preceded by dysplastic changes of the metaplastic mucosa. As mucin expression changes during neoplastic progression, they represent candidate molecular markers for the various stages of this process. The objective of this study was to determine the expression pattern of the mucins in neoplastic Barrett's epithelium. From the majority of the 22 patients diagnosed with an Barrett's esophagus included in this study (mean age 68 years), both biopsy samples from the squamous epithelium and the Barrett's epithelium were included. Furthermore adenocarcinoma biopsies from 12 of these patients and high-grade dysplasia biopsies from 5 of these patients were included. Mucin expression was determined by RT-PCR. Changes in expression levels are observed for all mucins during the development of an adenocarcinoma. Muc3, Muc5AC, Muc5B and Muc6 are expressed in none of the squamous epithelium samples, almost all BE samples and high-grade dysplasias and in about half of the carcinoma samples. Muc1 and Muc2 also follow this pattern, but the differences are less distinguished. The most striking difference is the upregulation of Muc4 and Muc6 in high-grade dysplasia. Muc4 was present in 58% (n=17) of BE samples and 80% (n=5) of high-grade dysplasia samples. Muc6 expression was found in 76% of BE samples and in 100% of high-grade dysplasia samples. Mucin expression is currently analyzed at protein level to confirm these results.
Conclusions: Mucin expression changes during the development of an esophageal adenocarcinoma. Muc4 and Muc6 could serve as early tumormarkers in this process.

Cdx2 expression is an early marker for the development of Barrett's esophagus

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Barrett's esophagus (BE) is characterised by the replacement of the squamous epithelium of the esophagus by epithelium of the intestinal type. The genetic events responsible for this trans-differentiation are poorly understood. We postulated that Cdx2 expression could be an early marker of transdifferentiation in BE since Cdx2 expression has been detected in intestinal metaplasia (IM) of the stomach and in normal appearing gastric mucosa directly surrounding the IM region.
Cdx2 expression was determined by reverse transcriptase polymerase chain reaction (RT-PCR) in biopsies taken from columnar epithelium and squamous epithelium of the esophagus from 5 patients with BE, and in biopsies taken from the colon and ileum from 5 patients with normal findings at colonoscopy.
Cdx2 mRNA was present in all control tissues (colon and ileum biopsies). In addition, Cdx2 mRNA was present in all biopsies from Barrett's epithelium, but not in squamous epithelium of the esophagus. Immunohistochemical experiments are required to localise Cdx2 expression in the columnar-squamous epithelial junction.
Conclusion: Cdx2 transcription is present in BE and absent in the squamous epithelium of the esophagus. Therefore, the presence of Cdx2 expression in histological normal squamous epithelium of the esophagus, may represent a novel early marker for the development of BE, which can be used to prospectively follow patients with esophagitis with Cdx2 expression to see if they develop BE.

Mechanisms underlying mucosal tolerance in the gastro-intestinal tract (Final report MLDS-project)

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Food allergy is characterized by a disturbance of the natural immunologic tolerance to harmless dietary antigens that enter the gastro-intestinal tract. As a result of this disturbance a preferential development of Th2 cytokine responses occurs, associated with increased allergen specific IgE levels and mast cell degranulation, that may ultimately lead to symptoms ranging from eczema to septic shock. The cause of the disturbance of the natural immunologic tolerance remains unclear and is complicated by the lack of knowledge on the precise mechanisms that underlie oral tolerance under homeostatic conditions. Therefore, the focus of our research is to unravel which factors are crucial for mucosal tolerance and identify whether and how these factors are changed under allergic circumstances.

After oral administration of ovalbumin (OVA) in mice, the first OVA-specific T cell responses can be observed in the Peyers patches (PP) and mesenteric LN (MLN) within 72h after feeding. Isolation of specific T- cell subsets from PP and MLN and transfer to naive mice revealed that within 48h of OVA feeding functional Tr cells develop. This Tr induction results from an interaction between an OVA presenting dendritic cell (DC) and naive T-cells under the influence of the microenvironment in the gut mucosa. Modulating this environment by inhibition of the cyclooxygenase-2 dependent arachidonic acid metabolism dramatically suppressed induction of oral tolerance. This failure of tolerance induction could be attributed to dysfunctional Tr induction in the MLN and PP, which surprisingly was not associated with any major changes in the number of divisions and phenotype of OVA responder T-cells. Whether cyclo-oxygenase-2 inhibition caused changes in conditions of antigen presentation that account for the defective Tr induction is currently under investigation.

Further identification of Tr cells and insight into their activation will lead to application in downregulation of immune disorders in the gut.

Linkage analysis of colitis susceptibility in Gαi2 deficient mice unravel new loci in chromosomes not previously found in other models of experimental colitis

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Genetic analysis of colitis susceptibility in inbred strains of mice may contribute to unravel the complex genetic basis of human inflammatory bowel disease (IBD). The Gαi2 protein is involved in suppressing Th1 responses and IL-12 production. Gαi2 deficient C3H/HeN mice spontaneously develop an IL-12 dependent Th1 mediated inflammation, resembling IBD in humans. On the contrary, C57BL/6 mice with the same mutation do not. These strain differences in colitis susceptibility offer the opportunity to identify chromosomal regions and genes that mediate these differences in colitis susceptibility.

Gαi2 deficient C3H/HeN mice were crossed with Gαi2 deficient C57BL/6 mice. The F1 population was intercrossed to generate a group of 150 Gαi2 deficient F2 mice. The F2 population was monitored for the development of colitis using clinical, serological and histological parameters. Resistant and susceptible mice were subjected to a genome-wide screen using 138 microsatellite markers.
Genetic analysis of the phenotypic extremes (n=85) in the F2 population revealed a locus on chromosome 1 at 62 cM that exceeded the threshold for significant linkage in a genome-wide screen ($P < 0.0005$; Chi2 = 15.6). In addition, loci on proximal chromosome 9 (at 9 cM) and distal chromosome 13 (at 71 cM) were identified that exhibited suggestive linkage ($P < 0.005$). The loci on chromosomes 9 and 13 are strongly skewed towards the female and male gender, respectively.
Conclusion: A region on chromosome 1 harbors a gene that mediates susceptibility to colitis in Gαi2 deficient mice. Candidate genes within this region include IL-10 and Cxcr4. The identification of multiple genetic loci not previously found in other experimental colitis models adds to the complexity and heterogeneity underlying susceptibility to colitis and illustrates why identification of genes underlying human IBD has proven to be so difficult. Studies to identify the actual disease causing mutations are underway.

Mitogenic signaling in intestinal cells suppresses guanylyl cyclase C expression by phosphorylation of CDX-2 at serine 60 *

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Guanylyl cyclase C (GC-C) inhibits intestinal cell proliferation upon activation by specific ligands (guanylin, ST). CDX-2 is a critical transcription factor required for the expression of GC-C. Phosphorylation of CDX-2 at serine 60, which is mediated by mitogen-activated protein kinase kinase (MEK), reduces its transactivating capacity. GC-C expression is characterized by an increasing gradient along the crypt/villus axis, opposing that of phosphorylated CDX-2 at serine 60. We investigated whether mitogenic signaling reduces transactivation of GC-C expression through phosphorylation of CDX-2 at serine 60 *in vitro*. Experiments were conducted utilizing intestinal epithelial cell lines, CDX-2 expression vectors, pharmacological treatments, GC-C promoter-luciferase reporter gene assays, FLAG-CDX-2-immunoprecipitations and specific anti-phospho-serine 60-CDX-2 immunoblots. GC-C promoter transactivation is enhanced by co-expression with the phosphorylation-incompetent CDX-2 S60A mutant compared to wild-type CDX-2 in intestinal cells that phosphorylate CDX-2 at serine 60. Mitogen-induced signaling by phorbol ester (PMA) induced phosphorylation of CDX-2 at serine 60 and inhibited transactivation of the GC-C promoter-luciferase construct in T84 cells. PMA reduced endogenous expression of GC-C mRNA, ST receptor binding sites, and ST-stimulated cGMP accumulation in T84 cells. CDX-2 phosphorylation and the associated reduction in GC-C promoter activity induced by PMA were mediated by a calcium-independent isoform of protein kinase C (PKC) and by MEK. Phosphorylation of CDX-2 at serine 60 reduces GC-C expression. Mitogenic signaling induced by PMA reciprocally suppresses GC-C expression via phosphorylation of CDX-2 at serine 60. These studies start to define the relationship between mitogenic signaling and the CDX-2-dependent GC-C expression in the transition from proliferating progenitor cells to differentiated enterocyte along the crypt-villus axis in the intestine.

Dual role of Toll-like receptor (TLR)4 in septic peritonitis in mice: protection by TLR4 during initial infection is lost when peritonitis complicates acute pancreatitis

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Pancreatitis is frequently complicated by Gram-negative infections. TLR4 plays a major role in the antibacterial host defense against Gram-negative infection; however, little is known about the role of TLR4 during infections complicating critical illness such as pancreatitis. Aim: To determine the influence of pancreatitis on the host response to abdominal sepsis caused by Escherichia coli in TLR4 competent and deficient mice. Methods: Wild type (Wt, C3H/HeN) and TLR4 mutant (C3H/HeJ) mice received an intraperitoneal injection with 5*104 CFU E.coli, preceded by 12 hourly injections of either cerulein (50ug/kg/hour) to induce pancreatitis or saline (sham). Results: TLR4 deficient mice subjected to peritonitis displayed a reduced ability to clear E.coli, as reflected by more CFU in peritoneal lavage fluid, liver and blood (all $P<0.05$ vs Wt). In separate experiments, pancreatitis developed comparably in Wt and TLR4 mutant mice. If peritonitis was preceded by acute pancreatitis, there was a marked decrease in host defense in Wt mice (CFU in PLF, blood and liver all higher in pancreatitis/peritonitis mice, $P<0.05$ vs sham/peritonitis); however, this decreased host defense was absent in TLR4 mutant mice with pancreatitis/peritonitis. Conclusions: 1. TLR4 is important for host defense against E.coli induced septic peritonitis. 2. Pancreatitis reduces host defense to abdominal sepsis caused by E.coli in Wt mice. 3. The role of TLR4 in host defense against E.coli peritonitis is lost if this infection complicates pancreatitis

Opposite effects of phospholipid and cholesterol incorporation into bile salt micelles on ABCA1 and ABCG1 expression in CaCo2 cells: implications for intestinal cholesterol absorption

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Intraluminal solubilization of cholesterol into bile salt micelles enhances its absorption into intestinal cells. Additional incorporation of phospholipid inhibits cholesterol absorption. Apical heterodimer proteins ABCG5 and ABCG8 may pump cholesterol back to the intestinal lumen, whereas ABCA1 and ABCG1 appear to enhance transfer of the sterol from the basolateral intestinal cell membrane into circulating HDL particles. We studied effects of varying micellar composition on expression of various ABC transporters. CaCo-2 cells were incubated overnight with micelles containing: taurocholate and cholesterol: taurocholate and egg yolk phosphatidylcholine with or without cholesterol: taurocholate, sphingomyelin and cholesterol: or PBS (control). RNA expression of ABCA1, ABCG1, ABCG5, ABCG8 and ("housekeeping" enzyme) GAPDH were then quantified by real time PCR (light cycler technology). ABCA1 expression was 2-3 fold decreased by incubation with phospholipid-containing micelles regardless type of phospholipid, with or without cholesterol. ABCG1 expression also tended to decrease under these circumstances. In contrast, when CaCo-2 cells were incubated with taurocholate-cholesterol micelles in the absence of phospholipid, ABCG1 expression increased 2-3 fold. There was no change of ABCA1 expression under these circumstances. There was no effect of various micellar incubations on GAPDH expression. ABCG5 and ABCG8 were present in low abundance, and difficult to detect, with or without micellar incubation.
Conclusions: micellar incorporation of phospholipid in bile salt micelles inhibits ABCA1/G1 expression, whereas cholesterol incorporation in bile salt micelles enhances ABCG1 expression. Regardless the underlying mechanism (either effects on thermodynamic activity and availability of the sterol or intracellular signalling effects), our findings indicate an important role of micellar composition in the intestinal lumen on pivotal intestinal ABC transport proteins.

Helicobacter pylori is sensitive to nickel only at acidic pH

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As most antibiotics do not perform well in the acidic environment of the stomach, antibiotic treatment of *Helicobacter pylori* infection is often combined with proton pump inhibitors (PPIs) to increase the gastric pH. Transition metals can have antimicrobial properties, and their biological availability is known to be affected by pH. Therefore the sensitivity of *H. pylori* to a range of metals was determined at neutral pH (7.0) and compared with the sensitivity at acidic pH (5.5). *H. pylori* reference strain 26695 was grown in Brucella media supplemented with 1% β-cyclodextrins. Medium pH was adjusted to either pH 7.0 and pH 5.5 using hydrochloric acid, and subsequently metal chlorides were added to final concentrations ranging from 1 - 1000 µM. Metals tested were bismuth, cadmium, cobalt, copper, iron, manganese, nickel and zinc. Bismuth and cobalt displayed the highest level of toxicity to *H. pylori*, as growth was inhibited at concentrations of < 1 µM bismuth and < 3 µM cobalt, respectively. Cadmium was toxic at concentrations of < 50 µM, while zinc, copper, manganese or iron at concentrations upto 500 µM did not affect growth of *H. pylori*. Only with nickel there was pH-dependent toxicity: at pH 7.0, supplementation with nickel upto 1000 µM did not affect growth of *H. pylori*, whereas in contrast at pH 5.5 nickel concentrations of 10 µM already completely inhibited growth. **Conclusion**: *H. pylori* displays a dramatic increase in sensitivity to nickel at pH 5.5, which is the average pH thought to occur in the gastric mucus layer where *H. pylori* resides. While nickel itself may not be a suitable therapeutical compound, elucidation of the mechanisms underlying nickel-sensitivity may allow for the development of a new class of antimicrobial agents which function at acidic pH, and thus can be administered without acid-suppressive drugs.

Identification of neurotensin binding sites: Neurotensin receptor-1 and -3 are expressed in human gastrointestinal tract

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Neurotensin (NT) a neuropeptide of the gastrointestinal tract is involved in the regulation of motility and inflammation. Three receptors for NT are identified; two (NTR1, NTR2) belong to the G protein-coupled receptor family whereas the third (NTR3) is structurally unrelated. Recently Martin et al (Gastroenterology 2002) reported heterodimer formation of NTR1 and NTR3 in cell lines. In human intestine there is only limited data about the expression pattern of the different NT receptor types. In a previous study a decrease was shown in the amount of NT binding sites in patients with inflammatory bowel disease (IBD). The aim of the present study was to get information about which NT receptor types are present in the human gastrointestinal tract of IBD and control patients. The affinity constant (Kd) of NT binding was measured by cold saturation studies and mRNA levels of NTR1 and NTR3 were studied with RT-PCR. Human tissue (colon and ileum) was obtained from surgical specimens of patients with adenocarcinoma (controls) or IBD.
As expected there was no difference between the Kd's measured in the different tissues, the overall mean was 1.55±0.83 nM. This Kd is comparable with the Kd found for NTR1 and NTR3 in literature but excludes the presence of NTR2. With RT-PCR mRNA of NTR3 was detected in all examined tissue, but NTR1 was not always present in detectable levels. NTR1 mRNA expression was limited to the mucosa of control colon and all samples with smooth muscle. If both receptors were expressed, the amount of NTR3 mRNA exceeded always that of NTR1.
In conclusion in human gastrointestinal tract no NTR2 expression is found. Human NT binding to smooth muscle is due to the presence of both NTR1 and NTR3, while in mucosa NTR1 is not present in ileum and inflamed mucosa. These results suggest that in human in smooth muscle but not in ileal mucosa heterodimers could be formed.

Quality of Life in children with inflammatory bowel disease: psychometric properties of the Dutch Impact questionnaire, coping strategies and parent-child differences (Final report MLDS-project) *

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The aim was to describe the psychometric characteristics of the Impact, a new disease specific quality of life (QoL) instrument for children with inflammatory bowel disease (IBD); to assess the relation between disease activity and QoL; to describe coping styles children with IBD use; to assess parent-child differences in reporting of the child's QoL.
83 Children with IBD, ranging from 8 to 17 years old (response rate 66%) completed the Impact questionnaire containing 35 items on 6 domains. In addition, children and one of their parents completed a generic QoL instrument. Disease activity was measured with a 5-item symptom card. Coping styles were assessed using two instruments: a generic and a disease-related instrument.
Reliability and internal consistency were good for the Impact questionnaire (Cronbach's alpha's for the domains: .57-.86; intra-class correlation coefficients: .67-.91); discriminant validity was good between children in groups of disease activity and disease course severity; convergent validity with the generic instrument was satis-factory. Children with more active disease reported a significantly lower QoL than children with inactive disease on all domains. In comparison with healthy children, children with IBD use more avoidant coping. The use of predictive coping (positive thinking) was associated with a better QoL. Parents reported lower QoL than did children themselves. Agreement between child and parent was highest on objective domains of life (correlation coefficients: .73-.83), where agreement was lower on subjective domains (coeffi-cients: .51-.62).
Conclusions: The Impact is a valid and reliable instrument to measure QoL of children with IBD. QoL is highly related to disease activity and coping styles. Parents are adequate raters of the child's QoL, however they tend to underestimate the QoL as reported by the children themselves.

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Predictors of outcome in children and adults with achalasia treated with pneumo-dilation; A prospective study *

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We prospectively studied a large prospective cohort of patients with achalasia and analysed predictors of outcome of pneumodilation.
Between 1975-2001 392 patients were referred to our hospital with a clinical suspicion of achalasia. Following a strict diagnostic protocol 378 patients were diagnosed with primary achalasia and were treated with standard pneumo-dilation and followed according to a strict yearly protocol.
In this study we focus on presenting symptoms and clinical features. In previous studies pneumo-dilation was less successful in children, so we separated the data for children (under 17 years) and adults.
There were 26 patients under 17 years and 352 adults. The children presented a mean of 2.4 years after symptom onset, while adults did so after 6.2 years (p=0.01 t-test). Presenting symptoms in children and adults respectively were dysphagia (100/99%, n.s.), regurgitation (73/70%, n.s.), retrosternal pain (42/40%, n.s.), pyrosis (4/24%, p=0.01), cough (31/18%, n.s.) and weight loss (27/47% n.s.).
Esophageal manometry showed no difference between both groups. Barium swallow showed dilation in 65% and 81%(n.s.) Endoscopy showed dilation in 58% and 76% (p=0,05)and food retention in 77% and 74%(n.s.).
In 16 children pneumo-dilation failed after a mean 32 months, compared with 86 failures after a mean 38 months in adults (p=0.001).
Statistical analysis revealed only age as a predictor of outcome; in comparing the two groups as well as within the adult group younger age adversely effects success of pneumo-dilation.
Children generally present with similar clinical symptoms as adults, with exception of pyrosis. Diagnostic evaluation shows more frequent esophageal dilation in adults at barium swallow and endoscopy and the delay until diagnosis is shorter in children than in adults. Young age adversely affects outcome of pneumo-dilation (p=0.003), all other parameters are no predictors of balloon dilation outcome.

Functional defecation disorders in children (FGD's); the paediatric Rome-2 criteria revisite

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Recently, the first standardised criteria for FGD's were proposed in Rome. Data on practical applicability in paediatric defecation disorders are lacking.
Aim was to evaluate the prevalence of childhood FGD's using Rome II criteria: functional constipation (FC), functional fecal retention (FFR), functional non-retentive fecal soiling (FNRFS)and compare these data with the classical definitions of defecation disorders: paediatric constipation (PC) and solitary encopresis (SE).
Therefore patients with symptoms of constipation and/or encopresis were included. Before intake, patients recorded a bowel-diary-(defecation- , encopresis frequency, consistency and, size of stools). A standard questionnaire was obtained and physical examination performed.
198 consecutive patients (0.66-15.76 yrs; 131 male) were included. According to the Rome II criteria, 68%, 18% and 22% of patients fulfilled the criteria for FC, FFR and FNRFS, respectively. 75% and 17% fulfilled the criteria for PC and SE, respectively. 17 patients fulfilled FC and FFR simultaneously. Almost 20% of the patients fulfilling PC were not recognized as having FC or FFR by the Rome II criteria.
Conclusion: A substantial group of children fulfils both criteria for FC and FFR. In contrast to the literature, a minority of patients fulfils FFR criteria. Constipation as defined by FC & FFR criteria is underestimated whereas FNRFS is overestimated compared to the classical criteria. This might be due to the lack of important items such as physical examination, defecation frequency and encopresis in the current Rome-II criteria. These important features of paediatric FGD's should be incorporated in the next Rome-III criteria.

Celiac Disease in the Dutch general population

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We studied celiac disease (CD) in 50.760 individuals from 2 population-based studies performed in 3 Dutch cities between 1987-1997. Blood samples and information on diet, health and social aspects were available.
Diagnosed CD was studied by sending subjects who adhered to a gluten free diet an added survey on CD diagnosis. Undiagnosed CD was studied in a random sample of 1440 subjects by detection of anti-endomysial (AEA) and tissue transglutaminase (TGA) antibodies in plasma. HLA-typing was done if both tests were positive. Duodenal biopsies were not offered for reasons of anonimity. We assumed undiagnosed CD was present if AEA and TGA were positive in a subject expressing HLA-DQ2 or -8.
The prevalence of diagnosed, biopsy-proven CD was 1:6329 (3745-20.661), of undiagnosed CD 1:287 (123-862) and of all CD 1:275 (240-321). There were no significant differences between subjects with diagnosed and undiagnosed CD or between subjects with and without CD concerning: sex, age, height, body mass index, subjective well-being and employment status. Body weight was lower in diagnosed compared to undiagnosed CD (p=0.007). Menarche occurred later in females with CD compared to females without CD (p=0.02). 6/7 females with diagnosed CD and no females with undiagnosed CD had children. The number of children was comparable between females with and without CD.
Conclusions: No biopsies were performed in subjects with positive screening and matching HLA, but the chance that they do not have CD is very small. For epidemiological research of CD we suggest this is acceptable. CD is strongly underdiagnosed in the Netherlands. It is unclear why diagnosed CD patients have lower body weight than undiagnosed CD patients. Because of the small number of CD patients, differences or comparabilities between subjects with and without CD must be interpreted cautiously, but the difference in menarche between females with and without CD is in accordance with the literature.

Medical audit on local results of infliximab (IFM) therapy for active Crohn's disease (CD)

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IFM can be a successful treatment for CD. High cost led to a consensus on specific treatment conditions. Nevertheless local doctors may be more willing to administer IFM in response to the complaints of patients, rather than being led by in- and exclusion criteria of clinical trials or by this consensus. This may result in a different outcome in IFM-therapy in a local hospital, compared with published results from specialised groups. Medical auditing is a generally accepted method to review results of therapies in individual hospitals. The aim of this study was to compare the results of IFM-therapy in a local hospital with published results of routine patient care by a specialised clinic (AMC, Amsterdam). 32 patients (M/F:8/24, mean age:35y) with active luminal (24) or fistulous (8) CD received 150 IFM-infusions (mean 4,7/pt) as an induction and maintenance regimen using the consensus criteria. Only in relation to sex and localisation the characteristics of our patients were statistical comparable with those of the AMC-cohort. Azathioprine (AZA) was used as co-medication in 56% of our patients. In the AMC-cohort, beside AZA, also methotrexate was used as immunomodulator. Response rate was 67% in luminal disease and 75% in fistulous disease, which results did not differ significantly from those of the AMC-cohort. A better response was seen in patients on AZA (83%vs.50%;$p<0.05$). Side-effects were seen in 19% of our patients, in the AMC-cohort in 17%(NS).
Conclusion: Since most published results of IFM-therapy in CD are derived from trials and not from routine patient care, it is difficult to perform a medical audit on local results. Only one published cohort was usable, although patient characteristics and co-medication differed. Response results and side-effects did not differ significantly. Since IFM-therapy weighs heavy upon the pharmaceutical budget of local hospitals, a regular comparison of results with published data is advisable.

Completion proctectomy after laparoscopic emergency colectomy for Inflammatory Bowel Disease: a comparative study

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Aims: The aim of the study was to evaluate the feasibility of the completion proctectomy with ileal pouch anal anastomosis (IPAA), for inflammatory bowel disease, after laparoscopic colectomy through a Pfannenstiel incision.
Methods: Sixteen patients had a completion proctectomy with pouch reconstruction after an emergency laparoscopic-assisted colectomy for toxic colitis. Proctectomy and IPAA were done via the Pfannenstiel incision (7.5 cm). All patients were prospectively evaluated and compared with the results of a historical control group, viz. 40 patients after completion proctocolectomy and IPAA through a midline incision. Efficacy parameters were operating time, early and late morbidity, and post-operative hospital stay. Complications developing more than 3 months after surgery were considered to be late complications.
Results: Median operation time was longer in patients who had a completion proctectomy through a pfannenstiel (200 min) compared to a completion proctectomy through a midline incision (150 min); $p<0.01$. There was less early morbidity in the “Pfannenstiel” group compared to the “midline” group, although not significant. Also there were no differences for late complications between the two groups. The number of relaparotomies was also lower in the “Pfannenstiel” group compared to the “midline” group; 1 vs 4, $p<0.001$. In the “Pfannenstiel” group one patient was reoperated for anastomotic leakage, in the “midline” group this was done because of small bowel obstruction, small bowel ischaemia, rebleeding, and for a dysfunctioning stoma. Median hospital stay in the “Pfannenstiel group was 10 days, in the midline” group this was 15 days.
Conclusions: Completion proctocolectomy with pouch reconstruction through a Pfannenstiel incision is feasible and safe, although it is more difficult, reflected by a longer operating time. Morbidity and long-term results for both procedures are similar.

Efficacy and toxicity of 6-mercaptopurine in 30 patients with inflammatory bowel disease

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6-Mercaptopurine (6-MP) is metabolised to 6-MMP and 6-TG, responsible for hepatic and cytotoxicity respectively. There is discussion about the clinical usefulness of metabolite levels. However, proper pharmacokinetic data are lacking. Therefore, we performed a pharmacokinetic study and correlated 6-MP metabolite levels with efficacy and toxicity in 30 IBD out-patients at 0, 1, 2, 4 and 8 weeks after starting 6-MP 50 mg once daily. TPMT-genotyping was carried out also. Mean patient age was 41 years (range 19-68), 20 were male 10 were female, 19 were suffering from Crohn's disease (CD), 11 from ulcerative colitis (UC). 6-MP was given for active disease in 10 and steroid dependency in 20 patients. Seventeen patients (57%) completed the 8 week period. Reasons for drop-out were intolerance (n=2), leukopenia (n=4), hepatotoxicity (n=1), pancreatitis (n=3) and lack of data (n=3). Only for leukopenia, a significant correlation with TPMT background was observed with an increase in relative risk (RR) of 12.0 (CI95%: 1.7-92.3) for patients with mutant TPMT alleles. TPMT and drug intolerance, hepatic or pancreatic toxicity showed no correlation. Notably, first week 6-TG levels in all 4 patients with leukopenia were above 300 pmol/8x10E8 RBC. 6-MMP levels did not correlate with parameters for hepatic or pancreatic toxicity.

Five of 6 patients with active disease at baseline and clinical remission at week 8 had 6-TG levels above the recently proposed lower therapeutic limit of 235 pmol/8x10E8. Three of 4 patients with no improvement had levels below this threshold.

Our study indicates the usefulness of therapeutic drug monitoring of 6-MP. We suggest to measure thiopurine metabolite levels at week 1 (to prevent early toxicity: 6-TG < 300 pmol/8x10E8 RBC) and week 4 (to detect undertreatment or non-compliance: 6-TG > 250 and late toxicity: 6-TG < 500 pmol/8x10E8 RBC). In case of very high early 6-TG levels TPMT-genotyping is advised.

Maintenance treatment with 6-thioguanine over one year in IBD patients

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In IBD, the thiopurines azathioprine (AZA) and 6-mercaptopurine (6-MP) are used on a large scale. However, clinical use of these drugs is limited by their potential myelotoxicity and hepatotoxicity. The down-stream metabolite 6-thioguanine is a promising thiopurine with good short-term safety and efficacy. The aim of the study is to determine the one-year safety of 6-thioguanine in AZA or 6-MP intolerant IBD patients.
We conducted an open label pilot study in AZA or 6-MP intolerant IBD patients. 6-Thioguanine was administered as maintenance treatment in a daily dose of 10 to 40mg. Adverse events and laboratory parameters were obtained during a one-year period in 36 patients.
Over the period of one year, no clinically relevant myelotoxicity was observed. An increase of liver enzymes above the normal range during the one year period were observed in 5 patients. This was explained by symptomatic choledocholithiasis in one patient and by steatosis hepatis without focal regenerative hyperplasia in histology in one patient. In another patient elevated liver enzymes were accompanied by an increase in serum amylase as previously seen on AZA. He refused a liver biopsy. In none of the patients, radio-logical signs of portal hypertension were seen. None of the patients discontinued 6-thioguanine due to lack of efficacy.
In conclusion: Maintenance treatment with 6-thioguanine is feasible in AZA or 6-MP intolerant IBD patients without relevant myelo-toxicity. Possibly drug related elevation of liver enzymes were seen in 3 out of 36 patients in the one year period without signs of portal hypertension.

No predictive value of TPMT genotyping for leukopenia or hepatotoxicity during azathioprine therapy in Inflammatory Bowel Disease

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Thiopurines have been correlated with dose-related hematological and hepatic toxic events. TPMT is largely responsible for metabolizing thiopurines, and is under control of common genetic polymorphisms. It remains unclear if TPMT correlates with toxicity and metabolite production, therefore we investigated if genotyping was necessary for optimizing therapeutic management.
TPMT genotyping was performed in 534 IBD patients for the most common mutations G238C, G460A and A719G leading to the alleles TPMT*2, TPMT*3A, TPMT*3B and TPMT*3C. In patients known to have TPMT mutant alleles, metabolite measurements were performed (6-TGN and 6-MMP), each patient was then matched with two controls having wild-type TPMT.
In 534 patients, wild type alleles were present in 481 (90%), 53 (9.9%) were heterozygous and 2 (0.04%) were homozygous which corresponds with previously reported allelic frequencies. In UC, we found 168 (88 %) wild-type alleles, 22 (11%) heterozygous and no homozygous patients.
Azathioprine was discontinued in because of non-allergic side-effects in 21 wild types (4%), 4 heterozygous (8%) and 1 homozygous patient (ns). Patients with mutant alleles had a relative risk of 1.49 (CI95%: 0.70-3.16) of having an episode of leukopenia (leucocytes < 4.0 x 10e9) and a relative risk of 1.53 (CI95%: 0.82-2.8) of having an episode of hepatotoxicity (ASAT > 40 U/L and/or ALAT > 50 U/L). Significant differences were found for RBC 6-TG level and 6-MMP/6-TG ratio ($p<0,05$) between patients with mutant- and wild type alleles, but not for RBC 6-MMP level. Three patients appeared non-compliers, with undetectable metabolite levels.
In this large cohort of IBD patients, we did not find a significant correlation between non-allergic side-effects and TPMT genotypes. This suggests that the TPMT genotype is not predictive of an individual's dominant metabolic pathway. In contrast to other studies, we did observe a significant correlation between TPMT genotype and 6-TG levels.

Comparison between gastric barostat and SPECT scanning to detect gastric relaxation

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Single Photon Emission Computed Tomography (SPECT) scanning has been suggested as a non-invasive alternative for the barostat to assess meal-induced fundic accommodation. However, whether this also applies for the detection of changes in gastric volume induced by a relaxant agent, remains questionable. Therefore we compared the capacity to detect changes in gastric volume evoked by meal ingestion with that induced by glucagon. After an overnight fast, healthy volunteers (13 f, 8 m; mean age 25 y. (18-54 y.)) underwent a barostat study and SPECT scanning on two separate days to assess meal-induced fundic accommodation (Nutridrink, 200 ml, 300 kcal) (n=17) or fundic relaxation to 1 mg i.v. glucagon (n=4). Meal-induced fundic relaxation (183 ± 10 ml vs. 289 ± 46 ml, p=0.05) and postprandial/fasting ratio (2.32 ± 0.10 vs. 2.27 ± 0.29, p=0.9) were not significantly different between SPECT scanning and barostat. In contrast, the glucagon-induced fundic relaxation (19 ± 5 ml vs. 406 ± 56 ml, p=0.007) and postprandial/fasting ratio (1.16 ± 0.03 vs. 3.02 ± 0.54, p=0.046) were both significantly lower for SPECT scanning compared to the barostat. The barostat/SPECT ratio was significantly lower for meal-induced accommodation compared to glucagon-induced accommodation (1.8 ± 0.4 vs. 26.0 ± 7.3; p=0.002 Mann-Whitney U test).
Conclusion: In contrast to the increase in gastric volume after meal ingestion, SPECT scanning failed to detect the profound relaxation evoked by glucagon. These findings suggest that SPECT scanning rather reflects the volume of the ingested meal than change in gastric wall tone, thereby questioning its usefulness to assess gastric relaxation per se.

Relation of partial gastric volumes and upper gastrointestinal sensations in patients with functional dyspepsia and healthy volunteers measured with 3-dimensional ultrasonograph

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3D ultrasound is a technique to measure gastric volume. Our aim was to investigate the relation between total and partial gastric volume changes and sensations in patients with functional dyspepsia and healthy volunteers.
12 patients (5 male, age 40.7±14) and 15 healthy volunteers (6 male, age 26.8±7) participated. 2D ultrasonographic images of the total stomach were acquired. A magnet and a probe sensor enabled 3D orientation. Epigastric pain, fullness, nausea and hunger were scored using a VAS. Subjects ingested 500ml (200ml Nutridrink+300ml water, 300kCal) within 3 min. Data were acquired at t=0 and 5,15,30,45,60 min postprandially. Gastric wall was outlined manually and total gastric volume was calculated, subsequently proximal gastric volume (10cm downward from diaphragm) and distal gastric volume (between pylorus and antral area landmarks) were calculated from total gastric volumes. Relationships were assessed using partial correlation, controlling for subjects.
Mean fasting gastric volume in patients (37.0±7.7ml) was comparable to healthy volunteers (32.5±2.5ml, p=NS). In addition, no differences in gastric volume were observed 5 min postprandially (506.7±6.9ml vs. 494.6±6.4ml, p=NS). The increase in total gastric volume was related to the increase in fullness in patients ($r=0.47$, $p<0.001$) and healthy volunteers ($r=0.53$, $p<0.001$). An even stronger correlation between increase in distal gastric volume and increase in fullness and hunger could be observed in patients ($r=0.74$, $p<0.001$, $r=-0.36$, $p=0.007$) and healthy volunteers ($r=0.79$, $p<0.001$, $r=0.34$, $p=0.003$). No relation was found between increase in proximal volume and increase in fullness and hunger in patients ($r=0.19$, $r=-0.001$, p=NS) and healthy volunteers ($r=0.18$, $r=-0.09$, p=NS).
Conclusions: The distal stomach rather than the proximal stomach plays the key role in the generation of upper gastrointestinal sensation fullness and hunger in patients with functional dyspepsia and healthy volunteers.

The effect of subcutaneous pegylated recombinant native human leptin on gastric emptying in man.

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Leptin, the ob gene product, is primarily produced by adipocytes but also at a lower level by gastric tissue. Recently, it has become clear that the stomach contains leptin receptors. Leptin plays an important role in the regulation of food intake and energy expenditure. It may reduce appetite, which could be related to changes in gastric emptying. However, it is not known whether leptin has a direct action on gastric emptying.
Ten healthy non-obese males (age 19-36 y) were included. Gastric emptying was measured in the morning at baseline, and 3 day after subcutaneous administration of a single dose of 80 mg long-acting pegylated human recombinant leptin (PEG-OB). It is known that peak serum levels are reached three day after administration*. Gastric emptying of a standardised solid test meal was measured using the ^{13}C-octanoic acid breath test. Serum leptin levels were measured at baseline and three days after leptin administration. Data were analysed using Wilcoxon's Signed Rank test.
The baseline serum leptin levels were 2.6 +/- 2.4 ng/ml. Three day after leptin administration the serum levels were 2111.4 +/- 555.1 ng/ml ($P<0.001$). No significant differences in gastric emptying could be observed. At baseline T1/2 was 98.9 +/- 55.9 min and Tlag was 51.8 +/- 37 min. Three day after leptin administration T1/2 was 81.0 +/- 34.5 min and Tlag was 29.9 +/- 24.5 min. P-values were 0.31 and 0.11, respectively.
Conclusions: Although there was a trend towards an accelerated gastric emptying, administration of 80 mg PEG-OB does not significantly affect the gastric emptying rate of a solid meal.

*Hukshorn et al. 2000. J Clin Endocrinol Metab 85:4003-4009.

Redefining the lag phase for solids using ^{13}C OBT and Doppler U

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In the scintigraphic gastric emptying (GE) test the lag phase ends when the radioisotope is detected in the ROI at the level of the duodenum. Recently the ^{13}C octanoic acid breath test (OBT) has been developed to measure GE. To calculate the lag phase for solids using OBT several mathematical models were developed, assuming that the lag phase calculated using this test is comparable to the lag phase seen using scintigraphy. This assumption is questionable since studies comparing both techniques show considerable ^{13}C excretion in breath 15 min after meal ingestion while no or only small amounts of radioisotope were detected at the level of the duodenum. The aim of our study was therefore to investigate whether transpyloric flow occurs during and directly after ingestion of a solid meal. We measured flow using doppler ultrasonography (US) in 6 healthy volunteers, during and after ingestion of a standard solid egg meal labeled with 100 mg ^{13}C octanoic acid (375 kCal). The OBT was performed simultaneously. An episode of GE was defined as flow across the pylorus with a mean velocity of more than 10 cm/sec lasting more than 1 sec. Breath samples were taken at regular intervals for 4 hours (the first 30 min every 2 min). The first emptying episode was seen after 7.06 min (median, range 3.55-16.10) after start of the meal ingestion. The number of GE episodes after 10 min was 2.5 (median, range 0-10), with a median cumulative GE time of 4 sec (range 0-26). The 13C OBT test showed a median absolute recovery of 0.4 micromol (0-1.5) after 10 min. A significant partial correlation between the absolute recovery of the 13C and cumulative GE time for the first 10 min($r=0.91$, $p<0.001$) was found.
Conclusion: Excretion of ^{13}C during and directly after ingestion of a solid meal can be explained by transpyloric flow, resulting in absorption and excretion of ^{13}C. The lag phase observed using the scintigraphic GE test can not be compared to the lag phase found with the OBT test.

Does Octreotide Influence Gastric Motor and Sensory Function in Functional Dyspepsia?

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Visceral hypersensitivity is an important feature of functional dyspepsia (FD). Symptoms in FD are provoked by meal ingestion, which causes chemical and mechanical stimulation of the gut. The somatostatin-analogue octreotide (OCT) may reduce dyspeptic symptoms in FD, but mechanisms of action remain poorly understood. Therefore we explored the effect of OCT on proximal gastric motor and sensory function in FD and healthy volunteers after mechanical, chemical and combined stimulation.
In a randomised, placebo-controlled design, 8 FD-patients (2M, age 21-58 yrs) and 8 healthy subjects (5M, age 19-25 yrs) were evaluated on two occasions, during iv. octreotide (25 µg/h) or saline.
We performed 1) mechanical stimulation with intragastric distensions (8-14 mmHg) using a barostat 2) chemical stimulation with intraduodenal fat (long-chain triglycerides; 120kCal/hr) and 3) combined stimulation. Symptoms were scored using visual analogue scales.
During distensions compliance did not differ between groups, nor between OCT and placebo. Fullness increased in all subjects (24±4 to 50±6 mmHg). Nausea was higher in patients vs. controls at 14 mmHg (46±14 vs.13±7 mm; $p<0.05$).
Intraduodenal fat increased gastric volume in patients and controls (195±41 to 388±51mL;$p<0.05$). OCT impaired fat-induced gastric relaxation in controls (fat+placebo vs. fat+OCT: 430±49 vs.160±36 mL) but not in patients. Fullness increased in all subjects in response to fat. Nausea was higher in patients vs.controls (50±15 vs. 6±2 mm;$p<0.05$). During combined stimulation these differences were no longer observed.
Conclusion: Dyspeptic symptoms are provoked by both mechanical and chemical stimulation of the gut. FD is characterized by hypersensitivity during mechanical and chemical stimulation. In healthy controls OCT affects proximal gastric motor and sensory characteristics during chemical but not during mechanical stimulation. OCT has no effect on gastric motor and sensory function in patients with FD.

Influence of Corticotrophin Releasing Hormone on gastric sensitivity and motor function in healthy volunteers

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Visceral hypersensitivity and/or gastric accommodation to a meal are considered to be important mechanisms underlying functional dyspepsia (FD). As stress is one of the main triggers of FD symptoms, we evaluated the effect of the stress hormone, cortico-trophin releasing hormone (CRH) on proximal stomach function. After an overnight fast, 8 healthy volunteers (4 m, 4 f; age 23 y (20-25 y)) underwent a gastric barostat study on two separate days. After i.v. infusion of CRH (2.3 øg/kg/h) or saline a stepwise distension protocol was performed followed by ingestion of a liquid meal (Nutridrink, 200 ml, 300 kcal at MDP+2 mm Hg). Symptoms were scored every 5 min and during each distension step. Basal volume increased significantly after CRH infusion compared to placebo (116 ± 18 vs. 19 ± 15 ml, p=0.001; Student's t-test). The threshold for discomfort (10.0 ± 1.6 vs. 9.5 ± 0.7, p=0.7; Student's t-test) and meal-induced accommodation (320 ± 28 vs. 235 ± 54 ml, p=0.2; Student's t-test) were both not significantly altered by CRH infusion compared to placebo. Symptoms reported during baseline, fundic distension and after meal ingestion were not affected by CRH infusion.
Conclusion: In healthy volunteers, peripheral infusion of CRH reduces basal fundic tone, but has no effect on meal-induced accommodation. CRH did not affect visceral sensitivity to distension. Whether the response to CRH differs in FD, like in patients with irritable bowel syndrome, remains to be investigated.

Acid- and metal-responsive transcriptional induction of ammonia-producing enzymes in Helicobacter pylori

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The human pathogen Helicobacter pylori colonizes the acidic environment of the gastric mucosa. The response of H. pylori to acid shocks consists of the production of large amounts of ammonia via urease-mediated degradation of urea. However, the adaptive mechanisms allowing growth at mildly acidic conditions (pH of 5.5) are still poorly understood. Therefore the diverse effects of acidification and nickel supplementation on the expression of the H. pylori ammonia-producing enzymes urease, amidase and formamidase was analyzed. H. pylori strain 26695 was grown in Brucella media at pH 7.0 and pH 5.5 or in media supplemented with increasing concentrations of NiCl2. Only low levels of urease, amidase and formamidase activity were detected when H. pylori was grown at pH 7.0. However, when H. pylori was grown at pH 5.5, the activity of all three enzymes was increased three- to tenfold. The increase in enzyme activity levels corresponded with increased mRNA levels for the respective genes. At pH 7.0, medium acidification was mimicked by supplementation of growth media with NiCl2, as this led to similar induction of urease, amidase and formamidase activity. Mutation of the nikR gene, encoding the nickel-responsive activator of urease expression, resulted in reduction of acid-responsive induction of all three enzymes. The NikR regulator did not mediate regulation of amidase and formamidase directly, but affected these enzymes indirectly via a regulatory cascade which includes the iron-responsive regulator Fur.
Conclusion: Our results indicate that under acidic conditions, to which H. pylori is exposed in the human stomach, an increase in ammonia production may take place depending on urea and amide substrate availability. The use of a regulatory cascade to sense acidification of the environment allows finetuning of the H. pylori response to acid, and this modulation of acid-resistance may constitute a key factor in the chronicity of H. pylori infection.

Fibroblast-derived matrix metalloproteinases activate a potent neutrophil chemoattractant from intestinal epithelial cell

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The upregulation of matrix metalloproteinases (MMPs) in the inflamed gut has mainly been associated with mucosal degradation and ulceration. However, their *in vitro* capacity to specifically cleave inflammatory mediators indicates that MMPs may also have a profound immunoregulatory impact.
In this study, we assessed whether MMPs proteolytically modify intestinal epithelial chemokine signalling. Fully differentiated CaCo-2 cells were grown on filters, stimulated with IL-1β, and exposed basolaterally to nanomolar concentrations of activated MMP-3. Chemotaxis assays of the conditioned media revealed that MMP-3 dose-dependently induced the neutrophil, but not monocyte, chemoattractant capacity of CaCo-2 cells. A similar response was obtained when these cells were co-cultured with IL-1β-stimulated colonic fibroblasts (CCD-18co), which expressed various MMPs, including MMP-3, -10, and -12. The addition of doxycyclin, a broad-spectrum MMP inhibitor, disrupted the CaCo-2 chemotactic response. The principal mediator of these protease-related effects was identified as the potent neutrophil chemokine neutrophil activating peptide 2 (NAP-2, CXCL7), a cleavage product of biologically inactive platelet basic protein (PBP). Antibodies against NAP-2 greatly inhibited the MMP-induced chemotactic response, and PBP mRNA and protein was detected in stimulated CaCo-2, but not in CCD-18co cells. In addition, PBP transcripts could be detected in isolated epithelial cells from patients with inflammatory bowel disease, but not in the normal intestine.
Our data suggest that fibroblast-derived MMPs proteolytically activate the neutrophil chemokine NAP-2 from the intestinal epithelium, adding another dimension to MMP function and to our understanding of the pathogenesis of intestinal inflammation.

Hypoxia and reoxygenation primarily affect absorption relative to secretion, without changing barrier function in rat ileum *in vitro*

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Intestinal ischemia and reperfusion may lead to profuse secretion of water and electrolytes. The underlying mechanisms are still incompletely understood, and have been related to increased hydrostatic pressure, to denudation of intestinal villi and recently, to adenosine-mediated enhancement of chloride secretion.
We studied the effects of hypoxia and reoxygenation on baseline electrophysiological parameters, on cholinergically induced secretion by carbachol, on glucose-induced absorption, and on epithelial barrier function to small (disodium-fluorescein (Na2Fl, 0.3kD)) and large (horseradish peroxidase (HRP, 4.0kD)) molecules, in rat ileum mounted in Ussing chambers, to provide additional information about the underlying mechanisms of secretion after ischemia and reperfusion.
During 30 min of hypoxia the short circuit current (Isc) declined sharply from 65.8±7.5 to 2.8±2.8 μA/cm2, which recovered completely during 60 min of reoxygenation. Carbachol-induced Isc-changes decreased 2-fold, from 72.9±17.4 to 35±11.4 μA/cm2 (P=0.041), and glucose-induced Isc-changes decreased 10-fold, from 17.6±2.7 to 1.8±0.8 μA/cm2 (P=0.002), after 30 min of hypoxia and 60 min of reoxygenation. Steady-state values of Na2Fl- and HRP-fluxes did not change when subjected to 30, 60 or 90 min of hypoxia and subsequently reoxygenation compared to control values, reflecting an intact barrier function. We observed that 30 minutes of hypoxia followed by 60 minutes of reoxygenation affected glucose-induced absorption to 10±6 % of control values, and carbachol-induced secretion to 48±8 % of control values (P=0.015), in epithelium that is fully capable to maintain its barrier function to small and large permeability probes.
In conclusion, the differential effects of hypoxia and reoxygenation on intestinal absorption and secretion may lead to a prosecretory imbalance, which may contribute to the intraluminal fluid sequestration and diarrhea observed after intestinal ischemia and reperfusion.

Basolateral Ca^{2+} -dependent K^+ -channels play a key role in Cl^- secretion from colon mucosa by taurodeoxycholate (TD)

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The diarrhea associated with malabsorption of bile salts such as the secondary hydrophobic taurodeoxycholate (TDC) may be partly explained by the TDC-induced increase in colon Cl^- secretion. We, therefore, investigated the effects of TDC on electrical parameters and electrolyte transport of rat proximal colon mucosa mounted in Ussing chambers. Colonic secretion, measured as short circuit current (ISC), progressively increased (up to ΔI_{SC} 8.1±0.7 $\mu A/cm^2$, n=20) upon mucosal incubation with TDC ranging from 0.5 to 2 mM; up to TDC 2mM the effect was reversible with no changes in epithelial resistance (Rt), and lactate dehydrogenase (LDH) release. In contrast, for TDC >2 mM, I_{SC} increased further but the effect was not reversible and associated with a significant decrease in Rt and LDH release, implying a cytolytic effect. Mucosal preincubation with the Cl- channel inhibitor 5-nitro-2 -(3-phenylpropylamino) benzoic acid (NPPB), fully prevented the pre-cytolytic effect of TDC on I_{SC}. By contrast, the apical Na^+ channel inhibitor amiloride had no influence on TDC effects. Cl^- removal in the serosal bath as well as serosal preincubation with furosemide, a $Na^+/K^+/2Cl^-$ cotransporter inhibitor, significantly reduced TDC-induced increase in ISC. Inhibition of the basolateral Ca^{2+}-dependent K^+ channel -rSK4- with serosal clotrimazole or incubation with mucosal Ca^{2+}-free (EGTA) buffer completely prevented pre-cytolytic TDC-induced increase in I_{SC}. Conclusions: Cl^- secretion is activated in colon mucosa by TDC low concentrations; while at higher concentrations, a detergent cyto-toxic effect intervenes. Activation of the Ca^{2+}-dependent basolateral K^+ pathway through TDC-induced apical Ca^{2+} influx, provides the $Na^+/K^+/2Cl^-$ basolateral influx thereby the driving force for the apical exit of Cl^- ions. These findings further enhance the knowledge of the pathogenic mechanisms of diarrhea associated with bile salt mal-absorption.

Leucocyte matrix metalloproteinase (MMP)-9 gene and protein regulation in Crohn's disease

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Matrix metalloproteinase (MMP)-9 is involved in the pathogenesis of CD. Phagocytic cells are the main source of this cytokine inducible MMP. LPS is a potent stimulating factor for cells to express TNF-α and anti-TNF-α treatment is very effective in CD. We studied the role of LPS and TNF-α in the synthesis and secretion of MMP-9 by leucocytes from 8 CD patients and 5 healthy controls. Heparinized whole-blood was exposed to LPS (0.1µg/ml) for 1.5 h or 24 h, w/wo infliximab (*in vivo* for patients and *in vitro* controls) for 4-24 h. ELISA was used to determine MMP-9 protein levels and RT-PCR for MMP-9 mRNA, normalized for β2-microglobulin. Non-hematopoietic MMP-2 protein levels were used as protease controls. Short-term 1.5 h LPS stimulation increased MMP-9 levels in both CD patients and controls, to 1132 ng/ml (mean) and 364 ng/ml, respectively, both >2-fold higher than unstimulated samples, and CD significantly higher than controls. However, the respective MMP-9 mRNA levels were downregulated to 20% and 50% from that of unstimulated samples, whereas TNF-α mRNA was impressively increased. Infliximab did not affect the mRNA and protein levels of this short-term LPS stimulation. LPS stimulation for 24 h did not further increase the MMP-9 plasma levels of the CD patients, whereas in the healthy controls it raised to 679 ng/ml. The leucocyte MMP-9 mRNA levels, studied in healthy controls, simultaneously raised 16-fold. Infliximab did not affect protein but inhibited the MMP-9 mRNA induction by 80%, although 3-fold increased compared to unstimulated controls. MMP-2 levels were not affected by either LPS or infliximab.
Conclusions: Leucocyte MMP-9 is upregulated in patients with CD and immediately secreted upon LPS stimulation, without concurrent mRNA induction and unaffected by infliximab. Longterm stimulation induces MMP-9 mRNA synthesis which is TNF-α dependent. Thus, the enhanced leucocyte MMP-9 expression in CD seems to be regulated by TNF-α.

Cervical vagotomy aggravates experimental pancreatitis severity in mic

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Efferent vagus nerve pathways play an important role in the reduction of systemic inflammation during experimental endotoxemia. Aim: To determine the role of the vagus nerve in controlling local inflammation associated with acute pancreatitis. Methods: Acute pancreatitis was induced by 12 hourly intraperitoneal injections of the cholecystokinin analogue cerulein; all mice were sacrificed immediately thereafter. Twenty-four hours before the induction of acute pancreatitis, mice underwent either sham surgery, or a left sided cervical vagotomy. Three groups were compared, i.e A: Sham operation followed by 12 hourly ip saline injections, B: Sham operation followed by 12 hourly ip cerulein injections, and C: Left cervical vagotomy followed by 12 hourly ip cerulein injections. Severity of acute pancreatitis was assessed by measuring serum amylase and lipase, pancreatitis histology, myeloperoxidase (MPO), and pro- and anti-inflammatory cytokine levels. Results: Pancreatitis developed in all animals that received cerulein injections (all parameters, $P < 0.05$ A vs B/C). Mice subjected to left cervical vagotomy had significantly higher levels of plasma amylase (B: 16800 U/l vs C: 26380 IU/l, $P<0.05$) and lipase. Histopathological changes, relative pancreas weight, plasma IL-6 and pancreatic MPO content were all higher or more severe in vagotomized animals ($P<0.05$). Conclusion: Cervical vagotomy aggravates the severity of acute pancreatitis, indicating that intact vagus nerve pathways function to control excessive local inflammation during pancreatitis. These data provide the first evidence pointing towards neuroimmune interactions during experimental acute pancreatitis.

Of Mice and Man: Common H^+,K^+-ATPase T-cell epitopes in human and murine autoimmune gastritis

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Human autoimmune gastritis (AIG) is an organ-specific inflammatory disorder leading to hypochloridria, gastric atrophy and eventually to pernicious anemia. Gastric H^+,K^+-ATPase is the autoantigen in both human disease and experimental murine autoimmune gastritis (EAIG). Studies of EAIG significantly contributed to current knowledge of human AIG, but to what extent EAIG mimics AIG is still debated and the autoantigenic epitopes on molecular level in AIG are yet unknown. This study was performed to identify the H^+,K^+-ATPase epitopes recognized by gastric T-cell clones from AIG patients, and to define their TCR Vβ usage and epitope-induced cytokine response. 16 H^+,K^+-ATPase-reactive $CD4^+$ gastric T-cell clones obtained from 4 AIG patients were tested for proliferation to a library of overlapping 15-mer peptides comprising the α chain (spanned by 205 peptides) and β chain (spanned by 56 peptides) of H^+,K^+-ATPase. The repertoire of the TCR Vβ chain of H^+,K^+-ATPase-specific T helper clones was analyzed with a panel of 20 monoclonal antibodies and RT-PCR. Cytokine production of gastric T-cell clones in AIG upon recognition of their epitope was analyzed by ELISA. We identified 6 epitopes in the α chain and 5 epitopes in the β chain. 4 of the 11 (36%) H^+,K^+-ATPase epitopes recognized in AIG were found to overlap with epitopes that are relevant in EAIG, including a previously described epitope, which is highly conserved in mammals and sufficient to cause gastritis in mice. 12/16 autoreactive T-cell clones tested expressed different TCR Vβ chains. 14/16 (87.5%) T-cell clones produced IFN-γ, but not IL-4, which is consistent with the Th1 profile found in EAIG, whereas 2 clones produced both IFN-γ and IL-4, resembling a Th0 profile.
Conclusions: Our data suggest a striking similarity between human AIG and murine EAIG at the T-cell epitope level and with regard to cytokine secretion, and identical pathogenic mechanisms in human AIG and its experimental counterpart in mice.

Methotrexate and Infliximab act synergistic by inducing enhanced apoptosis in activated human lymphocytes

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Methotrexate (MTX) enhances the response to infliximab therapy in RA and psoriasis, although the mechanism of action is unknown. Recently, the MTX-infliximab combination therapy has been reported to be highly efficacious in Crohn's disease (CD). Since it has been shown that both MTX and infliximab induce apoptosis of activated immunocompetent cells, we hypothesize that the observed synergism acts through a potentiated effect on apoptosis of activated lymphocytes.
Peripheral blood lymphocytes were isolated from healthy volunteers using density gradient centrifugation and were stimulated for 24 hours with allogenic mature monocyte-derived dendritic cells (mixed lymphocyte reaction. Infliximab (100 ug/ml), a chimeric control antibody c17-1a (100 ug/ml), MTX (1 uM and 10 uM) and combinations of infliximab and MTX at both concentrations were added to the mixed lymphocyte reaction. Apoptosis was determined by FACS analysis after annexin V and 7AAD double staining. Data were statistically analyed using the student t-test.
Infliximab induced apoptosis in activated lymphocytes. Methotrexate concentrations of 1 and 10 uM induced apoptosis dose-dependently. Addition of infliximab increased apoptosis by 30% and 20% ($p<0.01$) for 1 and 10 uM respectively. Strikingly, the combination of infliximab and MTX was completely additive.
Conclusions: we observed an enhanced apoptosis of activated human lymphocytes using a combination of infliximab and MTX. Although the mechanism of action of these drugs remains to be elucidated the synergistic effect of these drugs suggest different mechanisms. This is clearly relevant for mucosal healing in CD, since therapeutic benefit has been associated with increased apoptosis of activated lamina propria T cells. A strong rationale now exists to further investigate the infliximab-MTX combination in a clinical setting.

Physiological consequences of short bowel syndrome in a piglet-model *

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Short bowel syndrome (SBS) is a complex disease entity arising due to a massive loss of the intestinal absorptive surface area. As a result, pathophysiological processes are initiated to compensate for bowel malabsorption and the resultant malnourished state. Much remains unclear about the processes involved, therefore we investigated various physiological parameters: body weight, fecal fat loss, biochemical parameters in serum (total protein, albumin, iron, magnesium, vitamin A and B_1), and glucose absorption by means of intestinal biopsies for electrophysiological measurements (Ussing Chamber), to monitor the effects induced by short bowel syndrome.
Piglets (9 weeks old): SBS-group (n=6) underwent 75% small intestinal resection (day 1), followed by intestinal biopsy (day 14) and termination (day 56). In Sham-group piglets (n=6) sham laparotomy (day 1) was performed, then intestinal biopsy (day 14) and finally termination (day 56).
At 56 days after resection there was significantly retarded growth in the SBS-group as compared to the Sham-group (51±2 vs 69±3kg *P*=<0.01), increased fecal fat loss (5.3±0.5 vs 2.7±0.5g fat/100g faeces *P*=<0.01), and hypoproteinaemic state (total protein: 44±1 vs 51±1g/L *P*=<0.01, and albumin: 24±1 vs 33±1g/L *P*=<0.01). Neither vitamins (Vit A: 1.3±0.2 vs 0.9±0.1 µmol/L, Vit B_1: 325±73 vs 329±15nmol/L) nor essential ions (Fe: 13±2 vs 15±2µmol/L, Mg: 0.76±0.04 vs 0.69±0.04mmol/L) showed significant change in either group. Ussing Chamber measurements showed reduced enterocyte glucose uptake in the SBS-group (% short circuit current change [Isc]: 25±5%) without change in the Sham-group (84±21%), over the experimental time course.
The results demonstrate that an effective SBS-model was obtained: following enterectomy, SBS-piglets demonstrated fat malabsorption and a malnourished (hypoproteinaemic) state with resultant growth retardation.

The Aquaporin-8 water channel (AQP8) is largely distributed in rat Gastrointestinal locations where large quantities of fluid are absorbed or secreted

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A remarkable amount of water is transported in the gastrointestinal (GI) organs to fulfil the secretory and absorptive functions of the GI tract. However, the molecular basis of water movement across GI epithelial barriers is poorly known. Important clues are provided by the recent identification of multiple AQP water channels in GI tissues. Here we define the mRNA and protein expression and the cellular and subcellular distribution of AQP8 in the rat GI tract. Methods: By semi-quantitative RT-PCR the AQP8 transcript was detected in duodenum, proximal jejunum, proximal colon, rectum, pancreas, liver and, to a lesser extent, in stomach and distal colon. Immunohistochemistry revealed AQP8 staining in the surface epithelial cells of duodenum, proximal jejunum, proximal colon and rectum where labeling was largely intracellular and confined to the subapical cytoplasm. In liver, AQP8 reactivity was found in intracellular membranes and, at lower extent, in the canalicular membrane. In pancreas, AQP8 immunostaining was also seen over the apical plasma membrane of the acinar cells. A complex pattern was observed by immunoblotting with membrane fractions of gastrointestinal portions incubated with affinity purified AQP8 antibodies. Conclusions: AQP8 distribution coincides exactly with GI locations where large quantities of fluid are transported daily, suggesting roles in intestinal water absorption/secretion, bile formation and bile flow, and secretion of pancreatic juice. The intracellular expression of AQP8 observed in most GI epithelia suggests its recycling between cytoplasm and plasma membrane and/or an involvement in the intracellular osmoregulation. Studies are in progress to further clarify whether AQP8 expression and distribution is similar in man in health and disease.

Troglitazone reduces fibrosis formation and progression in an experimental model of chronic pancreatitis in mice

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Peroxisome proliferator activated receptor gamma (PPAR-gamma) controls growth, differentiation, and inflammation. Aim: To determine the influence of troglitazone, a ligand for PPAR-gamma, on fibrosis and pancreatic damage in a mouse model of chronic pancreatitis. Methods: Mice received six hourly intraperitoneal injections with 50 mg/kg cerulein (to induce pancreatitis) or NACL (control), three times a week for six weeks. Seven weeks after the first injection all mice were sacrificed. Five groups were compared, i.e. A: NACL injections, B: NACL injections, chow mixed with 0.2% troglitazone, C: cerulein injections, D: cerulein injections, chow mixed with troglitazone, E: cerulein injections, chow mixed with troglitazone during last 3 weeks only. End points were pancreas weight, pancreas histology (abnormal architecture, glandular atrophy, pseudotubular complexes), collagen formation (sirius red staining to quantify fibrosis; image analysis), pancreas amylase and hydroxyproline content, TGF beta (in pancreas and plasma), and plasma soluble TNF receptor levels. The number of activated stellate cells was detected by immunohistochemistry. Results: Group C had developed chronic pancreatitis after 7 weeks (all parameters $P < 0.05$, C vs A). Troglitazone given either for seven weeks or only for the last three weeks, reduced pancreatic damage (histology, amylase and hydroxyproline content), collagen formation, TGF beta and sTNF receptor levels and the number of activated stellate cells ($P<0.05$, D or E vs C; nonsignificant for D vs E). Conclusion: Troglitazone blocks activation of pancreatic stellate cells and reduces fibrosis formation and pancreatic damage in experimental chronic pancreatitis. Troglitazone remains beneficial in a therapeutic setting when given after initial damage has been established.

Identification of Fur- and iron-regulated genes of Helicobacter pylori using whole-genome DNA array analysis

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Intracellular homeostasis of the essential nutrient iron is a necessity for all living organisms, since both iron-deficiency and iron-overload can cause cell death. The Fur protein is known to control bacterial iron homeostasis. The gastric pathogen Helicobacter pylori contains few regulators, but is able to adapt efficiently to the variable environment present in the human stomach. The aim of this study was to identify H. pylori genes regulated by iron and Fur. Gene expression was monitored with (i) the Eurogentec H. pylori DNA Array and (ii) Northern hybridization using RNA isolated from H. pylori 26695 wild-type and fur mutant cells grown under iron-restricted and iron-sufficient conditions. Protein expression was analysed using 2-dimensional (2D)-protein gel electrophoresis, and binding of Fur was monitored using a gel shift assay.
12 genes were identified that were repressed by Fur under iron-sufficient conditions. These include genes that are involved in metal metabolism (fecA1, fecA2, frpB1 and hp1432), nitrogen metabolism (amiE), motility (fliP), cell wall synthesis (murB), cofactor synthesis (pdxAJ, bioB). Conversely, 14 genes were repressed by Fur under iron-restricted conditions. These include genes that are putatively involved in iron storage (pfr), respiration (hydrogenase genes, cytochromes), tRNA synthesis (trpS), chemotaxis (cheV), oxygen scavenging (sodB) and finally the fur gene itself. The Fur- and iron-regulation of the sodB gene was confirmed using a gel shift assay, with recombinant H. pylori Fur, and was also present at the protein level on 2D-protein gels.
Conclusion: When compared to other bacteria, H. pylori Fur seems to have acquired novel functions in regulation of several metabolic pathways essential for gastric colonization. This suggests that Fur is a central regulator of H. pylori pathogenicity, and thus proteins regulated by Fur may represent targets for the development of antimicrobial prevention and intervention therapies.

Are transient lower esophageal sphincter relaxations (TLESRs) the most important mechanism of acid reflux exposure time in patients with gastroesophageal reflux disease (GERD)?

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In GERD patients gastroesophageal reflux is mainly associated with TLESRs and a low LES pressure (LESp) in > 70% and > 10%, respectively. However, the relationship between esophageal acid exposure and a TLESR has not yet been established. To elucidate this 2 data-sets were analyzed: A: stationary pH and manometry recordings performed in 36 GERD patients without hiatal hernia 3 h after a provocation test meal. B: 24-hour ambulatory manometry and pH recordings in 10 GERD patients without hiatal hernia. (A) In patients with GERD 74% of 411 reflux episodes in the postprandial state was associated with TLESRs representing 49% of the acid exposure time. A low LESp accounted for 16% of acid reflux episodes representing 41% of the acid exposure time. The acid exposure time per mechanism, hence, was significantly shorter for a TLESR (42 s) than for a period with low LESp (203 s, P<0.001). (B) During 24 hour, 69% of 337 reflux episodes in GERD patients was associated with a TLESR representing 51% of the acid exposure time. By contrast, a low LESp, responsible for 20% of reflux episodes, represented 38% of the acid exposure time. At night, 53% of 60 reflux episodes in GERD patients was associated with a TLESR representing 26% of the acid exposure time. A low LESp occurred in 36% of reflux episodes representing 71% of the acid exposure time. Postprandially, of 190 reflux episodes 75% occurred during a TLESR representing 53% of acid exposure time whereas a low LESp occurring in 17% of reflux episodes caused 38% of the acid exposure time. Acid exposure time per TLESR, hence, was significantly shorter than the acid exposure time per period with a low LESp during 24 hour (54 s vs 164 s; P<0.005), at night (43 s vs 335 s; P<0.03) and postprandially (49 s vs 140 s; P<0.001). Conclusion: The role of TLESRs as the most important mechanism underlying gastroesophageal reflux in GERD patients is over-estimated considering only their number not taking into account the acid exposure time.

The effect of Barrett's mucosa ablation with argon plasma coagulation (APC) on esophagogastric junction (EGJ) function.

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Although the efficacy of APC treatment for patients with Barrett's epithelium (BE) and high-grade dysplasia (HGD) has been demonstrated, the effect of APC on esophageal and EGJ motility has not been established. Six patients with BE and HGD who underwent APC therapy and 6 controls were studied. Patients underwent endoscopy at 2 years follow-up and concurrent esophageal manometry and pH metry with patients in fasting condition sitting upright for a period of 1 hour followed by a 2nd and a 3rd hour after meal ingestion (400 ml/450kcal). Mean amplitude of contractions in the distal esophagus was significantly higher ($P<0.001$) in APC treated patients, 64±8 mmHg, compared to 34±8 mmHg in BE patients. Velocity of peristaltic waves was not significantly different between patient groups ($P>0.05$). At fasting, mean EGJp (7.5±0.9 mmHg) in APC treated patients was not significantly different from the EGJp found in BE patients (6.7±1.1 mmHg) ($P>0.05$). In the 1st hour postprandially EGJp significantly decreased to 4.2±0.2 mmHg (APC: $P<0.02$) and 3.5±0.6 (BE: $P<0.03$), not being significantly different between patient groups ($P>0.05$). In the 2nd hour postprandially EGJp normalized in both groups. The fasting mean TLESR frequency in APC treated patients, 2.3±0.4/h, was comparable to the frequency found in BE patients, 2.2±0.6/h ($P>0.05$). TLESR frequency increased significantly in the 1st h postprandially to 5.8±0.4/h (APC: $P<0.001$) and 5.3±0.3/h (BE: $P<0.002$) and was not significantly different between patient groups ($P>0.05$). In the 2nd hour postprandially TLESR frequency normalized. Reflux frequency postprandially was not significantly different between APC and BE patients ($P>0.05$). Conclusions: 1) Esophageal motility is not impaired after APC. 2) Patients after APC exhibit a similar frequency of TLESRs both at fasting and after meal ingestion compared to BE patients 3) These findings suggest that APC does not affect the esophageal muscular layer and intramural nerve plexus.

Effects of growth hormone deficiency and recombinant growth hormone therapy on postprandial gallbladder motility and cholecystokinin release.

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Growth hormone (GH) plays an important role in intestinal cell proliferation. We aimed to evaluate effects of GH on cholecystokinin release and gallbladder contractility. Gallbladder and gastric emptying (by ultrasound) and cholecystokinin release were determined before and after 6 months recombinant human GH (rhGH) therapy in 12 patients with isolated GH-deficiency, either after mixed (n=5) or liquid (n=7) meal. Basal postprandial gallbladder contraction was severely impaired (19^{+}/-2% and 26^{+}/-3% of fasting volume after mixed resp. liquid meal). Intravenous cholecystokinin infusion to physiological postprandial levels induced moderate (53% and 49%) gallbladder contraction in two patients. Histology and cholecystokinin sulfation patterns in duodenal biopsies were normal in two other patients. After 6 months of rhGH therapy, fasting gallbladder volumes increased (from 20.8^{+}/-0.9 to 25.9^{+}/-1.1mL, $P<0.05$) and postprandial gallbladder emptying was restored (70^{+}/-6% and 70^{+}/-7% of fasting volume after mixed resp. liquid meal), without change of gastric emptying. Postprandial cholecystokinin secretion and gallbladder sensitivity to cholecystokinin were significantly enhanced during rhGH replacement compared to basal. Conclusions: Postprandial cholecystokinin release, gallbladder responsiveness to cholecystokinin and gallbladder emptying are severely impaired in absence of growth hormone. Reversibility during growth hormone suppletion suggests its involvement in regulation of gallbladder contractility.

Studies on the role of splanchnic innervation in visceral hypersensitivity associated with functional bowel disorders (Final report MLDS-project)

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Although there is no single mechanism responsible for the development of functional bowel disorders (FBDs), it is generally accepted that visceral hypersensitivity (HS) may play an important role in the pathogenesis of FBDs. Visceral HS could result from sensitization of primary afferent fibers, or sensitization of dorsal horn neurons. Here, we summarize the results of our recent studies evaluating the possible visceral analgesic properties of a variety of compounds, i.e. the NO-synthase inhibitor L-NMMA, the NMDA receptor antagonists dextromethorphan and ketamine and the selective serotonin reuptake inhibitor fluoxetine. Studies were performed in healthy volunteers (HV) and patients with functional dyspepsia (FD). In addition, because of the of the shared patho-physiological mechanisms with FD, we also studied patients with irritable bowel syndrome (IBS).
Results: L-NMMA did not alter the perception of sensations evoked by gastric distention in HV. However, L-NMMA increased basal gastric tone and reduced nutrient-induced gastric relaxation. In addition, L-NMMA triggered the onset of a phase III of the migrating motor complex. Both dextromethorphan and ketamine increased the sensitivity to gastric distention in HV without altering gastric tone or gastric wall compliance. Fluoxetine did not change the sensitivity to rectal distention, both in normosensitive and hypersensitive IBS patients, although hypersensitive subjects tended to report less severe abdominal pain after 6 weeks fluoxetine.
Conclusions: Blocking NO synthesis or NMDA receptors does not result in visceral analgesic effects in HV. However, this does not exclude an effect in conditions characterized by visceral HS such as FBDs. Therefore, studies evaluating L-NMMA and ketamine in FD and IBS are in progress. Furthermore, although IBS patients seem to benefit from treatment with fluoxetine, this was not associated with decreased sensitivity to rectal balloon distention, questioning the direct relationship between visceral hypersensitivity and symptoms in IBS.

Visceral perception health: Role of the N-methyl-D-aspartate (NMDA)- receptor

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Application of N-methyl-D-aspartate (NMDA)-receptor antagonists may hold promise for the treatment of visceral pain. Previously (AP&T 2002;16:1955-62) we demonstrated that dextromethorphan increased rather than decreased visceral sensitivity in healthy volunteers (HV). In this study we evaluated the effect on visceral sensitivity of S(+)-ketamine (S-Ket), another non-competitive NMDA-receptor antagonist yet with higher affinity to the receptor.
Methods: 12 HV (7M/5F) underwent a gastric barostat study after pretreatment with placebo, 25 mg and 50 mg S-Ket p.o. Studies were performed in a double blind randomized cross-over fashion. Sensations evoked by stepwise isobaric gastric distention (2 mm Hg/2 min above MDP) were scored on a 100-mm visual analogue scale. In addition fasting and postprandial fundic volume were measured at a fixed pressure level (MDP+2 mm Hg).
Results: Subjects receiving 50 mg S-Ket reached the threshold for discomfort / pain during gastric distention at significant lower distending pressures compared with 25 mg and placebo (P< 0.001, Kaplan-Meier log-rank test). In addition, the slopes of the pressure-sensation curves for bloating, nausea, satiation and pain were significantly increased by 50 mg S-Ket compared with 25 mg and placebo (P< 0.001, repeated measures ANOVA). S-Ket had no effects on fundic wall compliance (63±7; 66±5; and 78±4 mL/mm Hg for placebo, 25 and 50 mg, respectively, P= 0.2) or fundic volume (Fasting: 194±13; 179±19; and 213±19 mL for placebo, 25 and 50 mg, respectively, P= 0.4; Postprandial: 497±56, 464±57 and 448±77 mL for placebo, 25 and 50 mg, respectively, P= 0.8).
Conclusions: S-Ket, like dextromethorphan, increases visceral sensitivity in healthy volunteers. Taken together, these findings suggest the involvement of NMDA receptors in visceral perception. The role of NMDA receptors in conditions characterized by visceral hypersensitivity, such as functional bowel disorders, needs further study.

Lowered serotonergic activity changes cortical activation during painful rectal stimuli.

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Serotonin may be involved in visceral perception. IBS patients show altered cortical activation during painful rectal stimuli, compared to controls. Hence, the aim was to study the relation between visceral perception, cortical activation and serotonergic activity.
Eleven healthy females (19-25 y) were studied 3 times. Firstly, their individual visceral perception scores were obtained using a rectal barostat semirandom distension protocol. Subsequently, they were studied randomly under both a control condition and during lowered serotonergic activity. This was achieved by ingestion of 75 gr of a tryptophan (Trp)-free amino acid mixture. A Trp-containing mixture served as control. Firstly, an anatomical scan was obtained in a 1.5T MRI scanner. Rectal barostat stimuli consisted of 30 s intervals of 12 rest periods, 6 distensions with perception score 2 (mild urge) and 6 distensions with perception score 5 (painful urge) respectively, in random order. fMRI scanning (BOLD) was performed continuously. Data analysis using SPM99 for Matlab comprised calculation of both the z-scores and the size of the activated cluster (KE) of 3 regions of interest; the anterior cingulate cortex (ACC) and the sensory-motor cortex (GPrC and GpoC) left and right. The exact location of cortex activation was confirmed using Talairach's stereotaxic coordinates. For the painful urge stimuli the data were analysed for both conditions, and compared using Wilcoxon's Signed Rank test.
In the ACC both the activation and the size of the activated cluster were significantly lower in the Trp-depleted condition, compared to control (mean z-score: 0.47 vs. 2.90, P = 0.011, and mean KE: 1.1 vs. 1125, P = 0.008, respectively). In contrast, no significant differences in activation of the left and right sensory-motor cortex could be observed.
Conclusions: Lowering the serotonergic activity alters ACC activation. Whether this is directly related to the extent of perceived pain remains open.

Does a rectal barostatprocedure induce stress in IBS patients and healthy subjects?

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The barostat can be used to study the effect of stress on pressure-volume relations and visceral perception of the rectum. However, it is not known whether a rectal barostatprocedure (B) itself induces stress. Hence, the aim was to investigate whether a B induces stress in both irritable bowel syndrome patients (IP) and healthy subjects (HS).Twelve IP (9f, 3m, age31-69y) and 10 HS (10f, age18-27y) were studied twice. They underwent in random order either a 45 min B (staircase and semi-random protocol), or a rest period as a control condition. During both B and the control experiment salivary cortisol was measured at -15, 0, 15, 30, 45 and 60 min. The Profile of Mood States (POMS) measured changes in depression, tension, vigour, hostility and tiredness, simultaneously. Cognitive functioning (Word Learning Test, Word Recognition Test, the Verbal Fluency Test, and the Choice Reaction Task), was measured at 60 min in both experiments.
In HS the cortisol levels showed no significant difference between the experiments, (Wilcoxon $P>0.169$). However, in B the IP group showed a significant increase in cortisol ($P<0.03$) at t=0 (immediately after insertion of the barostat probe) and t=15 (after the staircase protocol). During B the HS showed a significant increase in the tension subscale of the POMS t = -15 (shortly before insertion of the barostat probe) and t=0 ($P=0.005$ and 0.017, respectively), as well as a significant decrease in the vigour subscale at t=45 and t=60 ($P=0.017$ and 0.028, respectively) compared to the control situation. In the patient group no changes in mood were observed. The cognitive tasks showed no significant differences between the experiments in both groups.
Conclusions: A rectal B induces a significant increase in salivary cortisol in IP but not in HS. The POMS showed that B in HS induces a significant increase in tension at the beginning of B, and a decrease in vigour at the end of B. The HPA-axis may be involved in IBS pathophysiology.

Irritable Bowel Syndrome in Ulcerative Colitis

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Many patients with ulcerative colitis (UC) in remission report abdominal symptoms, which resemble Irritable Bowel Syndrome (IBS). As IBS often develops after acute inflammation, e.g. gastro-enteritis, symptoms in UC in remission might originate from a post-inflammatory process. Our aim was to explore the prevalence of IBS-like symptoms and Quality of Life (QOL) in patients with chronic inflammation, i.e. UC patients with recent disease acitvity and those in remission.
Ninety-one UC patients were selected from colonoscopy records. Based on recent colonoscopy, patients were divided into a remission group (no activity within the last 12 months; UC-R) and a group with recent disease activity (within the last 12 months; UC-A). Sixty-three of 91 patients (35 F, age range 21-64 yr, average disease duration 13 yr) and 26 healthy volunteers (17 F, age range 18-65 yr) completed an IBS diagnostic questionnaire (Rome II), a validated QOL questionnaire (SF-36) and a 7-day diary on abdominal symptoms.
Six of 30 UC-R patients (20%) and 9 of 33 UC-A patients (27%) fulfilled Rome II criteria for IBS, compared to 5.8 % of the Dutch population ($p<0.001$). UC patients had more severe abdominal symptoms ($p<0.05$) and impaired QOL ($p<0.001$) compared to controls. Abdominal symptoms were more severe in both UC-A and UC-R patients compared to controls ($p<0.05$). QOL was impaired in UC-A patients ($p<0.001$), but not in UC-R patients. No differences were found in the occurrence of abdominal symptoms or in QOL between UC-A and UC-R patients. The presence or absence of IBS-like symptoms in UC-A and UC-R patients did not affect QOL.
Conclusion: In UC, the prevalence of IBS is significantly increased. Abdominal symptoms are more severe in UC patients compared to controls, irrespective of the presence or absence of IBS. QOL is impaired only in those patients with recently active disease. The presence of IBS does not further affect QOL.

IBS patients have a slower rectal adaptive relaxation than healthy controls, not related to serotonergic activity

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It is not known whether there is a difference in rectal adaptive relaxation (RAR) between IBS patients and healthy controls. It may be possible that the serotonergic system is involved in RAR.
Therefore, the aim was to study the RAR by means of a rectal barostat procedure in 14 diarrhea-predominant IBS patients (6 m, 8 f; 19-60 years) and 14 healthy subjects, matched for age, sex and BMI.
The participants were studied double-blinded in both a control condition and a tryptophan-depleted condition. This was achieved by ingestion of 75 g of a tryptophan-free amino acid mixture. A tryptophan-containing mixture served as a control condition. The participants underwent a rectal barostat procedure using an intermittent semi-random staircase distension protocol until maximal tolerable pressure. Each distension lasted 60s, and was followed by 30s baseline pressure (0 mmHg).
Rectal volume was measured at t=10s and t=60s after the start of each distension. The RAR (ml/s) was measured as the delta volume per second between t=10 and t=60, for each distension (P = 10, 15, 20, 25 mmHg). The data were analyzed using a repeated measures ANOVA.
The RAR increased significantly with increasing pressure in both patients and healthy subjects ($P<0.01$) in the control condition. The values ranged from 0.30 – 1.55 ml/sec. There was a significant difference between patients and healthy subjects in the control situation ($P=0.04$). The patients showed a slower RAR. Tryptophan depletion did not influence RAR in both the healthy controls and the patient group.
Conclusions: The RAR is determined by the pressure in the rectum. The RAR is slower in IBS patients, compared to healthy controls. Lowering the serotonergic activity does not alter RAR in diarrhea-predominant IBS patients or healthy controls.

Is rectal motor and sensory dysfunction in Irritable Bowel Syndrome subtype specific

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Visceral hypersensitivity and alterations in rectocolonic motility are key features in Irritable Bowel Syndrome (IBS). However, little is known on IBS-subgroup differences in rectal motor and sensory function, whereas these may reflect either common or different pathophysiology. Therefore, our aim was to investigate rectal motor and sensory function in large subsets of IBS-patients and in healthy controls.
Thirty-three healthy volunteers (22 F, age 43 ± 2.4 yr) and 95 IBS-patients (71 F, age 42 ± 1.4 yr, Rome II) were included; 32 diarrhea-type (IBS-D), 35 constipation-type (IBS-C) and 28 alternating type (IBS-A). A computerized barostat was used to perform a rectal pressure distension (1 mmHg increase per min, max 30 mmHg). Sensation of urge and pain was scored at regular intervals using Visual Analog Scales (0-10 cm). All subjects filled out a GI symptom diary for 7 days.
Minimal Distending Pressure was significantly higher in IBS-D compared to controls and IBS-C (14.5 ± 0.5 vs 12.9 ± 0.5 and 13.3 ± 0.4 mmHg respectively, $p<0.05$). Dynamic compliance, calculated over the steepest part of the pressure-volume curve, was significantly decreased in IBS-D (31 ± 2.6 ml/mmHg) and IBS-A (29 ± 2.6 ml/mmHg), but not in IBS-C patients (34 ± 2.2 ml/mmHg), compared to controls (43 ± 3.4 ml/mmHg, $p<0.01$). Thresholds for pain perception (> 1 cm on VAS score) in IBS-D (20 ± 1.8 mmHg) and IBS-A (22 ± 2.0 mmHg) were significantly decreased compared to IBS-C (26 ± 1.3 mmHg) and controls (30 ± 0.6 mmHg, $p<0.001$) and also in IBS-C compared to controls ($p<0.001$). Age, sex and diary symptoms of abdominal discomfort and pain were not correlated to rectal compliance and perception.
Conclusions: IBS-D and IBS-A patients, but not IBS-C patients, have increased rectal wall tone compared to controls. All patient subgroups have decreased perception thresholds but these differ between subgroups. These results point at IBS subtype specific differences in rectal motor and sensory function.

The involvement of interstitial cells of cajal in the rectoanal inhibitory reflex *

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Previous studies have suggested that interstitial cells of Cajal (ICC) act as mediator in nitrergic inhibitory neurotransmission. The aim was to examine the role of ICC and nitric oxide (NO) in the inhibitory neurotransmission of the murine internal anal sphincter (IAS). Anorectal manometry was performed using a micro-sized water perfused catheter in anesthetized mice. IAS relaxations were triggered by graded rectal distention (0.45–0.60 ml) using a polyethylene balloon. In addition, muscle strips of the IAS were mounted in organ baths for isometric tension recording. Relaxations were evoked by electrical field stimulation (EFS,0.25-8 Hz,1ms) in the presence of 1μM atropine and 1μM guanethidine. Rectal distention resulted in a volume-dependent relaxation of the IAS. The relaxations were significantly diminished in W/W^v mutant mice and nNOS-deficient mice compared to their wild type(WT) controls (0.55 ml:W/W^v mutant mice 10.1±4.8 vs WT 45.8±6.3%,n=10,p<0.05) (nNOS-deficient mice 32.9±6.0 vs WT 63.9±6.1%,n=10,p<0.05). In WT mice, relaxations were reduced by L-NAME(100 mg/kg, ip) (45.8±6.3 vs 29.8±6.6%,n=10,p<0.05). *In vitro*, EFS induced frequency-dependent relaxations of IAS muscle strips in W/W^v mice that were similar to their WT controls and that were reduced by L-NAME(200 μM)(8 Hz:W/W^v mice 0.16±0.02 vs W/W^v mice + L-NAME 0.03±0.02gr ,n=6,p<0.05). In nNOS-deficient mice, relaxations were reduced compared to their WT controls.

1. Our experiments illustrate the involvement of NO in the inhibitory innervation of the murine IAS. 2. Although the relaxations were impaired in the W/W^v mice in vivo, EFS-induced relaxations of muscle strips were comparable to that in WT mice. These findings argue against a significant role of ICC in the nitrergic neurotransmission of the murine IAS and suggest the possible involvement of ICC in mechanoperception. Morphological studies evaluating the distribution of ICC in the IAS are however necessary to confirm these conclusions.

PEG 3350 compared to Lactulose in the treatment of paediatric constipation. A double-blind, randomized controlled trial *

Wieger Voskuijl[1], Fleur de Lorijn[1], Wim Verwijs[2], Paul Hogeman[3], Jarom Heijmans[1], Jan Taminiau[1] and Marc Benninga[1] . Dept. of Paediatric Gastroenterology and Nutrition[1], Emma Childrens Hospital, Academic Medical Center, Amsterdam, Dept. of Paediatrics[2], Hofpoort Ziekenhuis, Woerden, Dept. of Paediatrics[3], Meander Medisch Centrum, Amersfoort, The Netherlands.

Treatment of childhood constipation mainly consists of longstanding laxative treatment. In the Netherlands, Lactulose is the laxative of first choice. Recently, Polyethylene glycol (PEG 3350, Transipeg) has been suggested as a good alternative laxative. Aim was to compare the clinical efficacy and side effects of PEG 3350 with Lactulose in childhood functional constipation treatment. Therefore 100 patients (age 6 mnths-15 yrs) with childhood constipation were included in a 8 weeks double-blind, randomized controlled trial. After fecal disimpaction, patients younger than 6 years received either Transipeg (3,75 gram/sachet) or Lactulose (6 gram/sachet), children older than 6 years started with 2 sachets/day. The dose was changed, depending on response (max 3/day). Primary outcome: defecation-, encopresis frequency, success after 8 weeks. Success was defined as encopresis less than once/2 weeks and a defecation frequency >3 per week. Secondary outcome: side effects after 8 weeks of treatment. 91 patients (49 male) completed the study. Both groups had an significant increase in defecation frequency (Transipeg 2.7-6.5/week, Lactulose 2.7-6.5/week) and a significant decrease in encopresis frequency (Transipeg 11.5-3.5/week, Lactulose 7.4-2.8/week). No differences in defecation and encopresis frequency were found between both groups. However, significantly more Transipeg-children were treated successfully (41%) compared to the Lactulose-group (22%)(p=0.02). Side effects like abdominal pain and flatulence did not differ significantly between the groups. Patients using Transipeg reported less straining (p=0.05) and pain at defecation (p=0.001). After one week of treatment significantly more children on Transipeg complained of the bad palatability of the compound (p=0.0001). After 8 weeks of treatment, this side effect had disappeared.
Conclusion: PEG 3350, compared to Lactulose, gives a higher success rate after 8 weeks of treatment with less side effects.

** De met asterisk gemerkte abstracts in dit programmaboekje zijn ingezonden voor de Sectie Kindergastroenterologie*

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