Programma najaarsvergadering 2 en 3 oktober 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

★

NEDERLANDSE VERENIGING VOOR HEPATOLOGIE

★

NEDERLANDSE VERENIGING VOOR GASTROINTESTINALE CHIRURGIE

★

NEDERLANDS GENOOTSCHAP VAN MAAG-DARM-LEVERARTSEN

★

NH KONINGSHOF

VELDHOVEN

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VOORWOORD

Hierbij treft u het volledige programma aan van de najaarsvergadering te Veldhoven, inclusief de samenvattingen van de voordrachten. De najaarsvergadering wordt zoals gebruikelijk weer voorafgegaan door het cursorisch onderwijs waarvan u op pagina 5 het volledige programma aantreft.

Naast vrije voordrachten door de verschillende secties en verenigingen, wordt op donderdagmiddag een minibattle verzorgd door de Nederlandse Vereniging voor Gastrointestinale Chirurgie, getiteld: 'ERCP versus laparoscopische choledochus exploratie voor CBD stenen'. Tevens wordt door de Sectie Maagdarmmotoriek een symposium georganiseerd getiteld: 'Gastroesophageale refluxziekte in de praktijk' en is er een symposium van de Nederlandse Vereniging voor Hepatologie: 'Nonalcoholic Steatohepatitis'.

Om 17.00 uur wordt in de Diezezaal de Altana Lecture gehouden. Deze lezing wordt verzorgd door Dr. P. de Groen. Aansluitend de ledenvergadering van de NVGE met de toekennning van het erelidmaatschap aan Prof. dr. C.B.H.W. Lamers. Alle leden worden van harte uitgenodigd hierbij aanwezig te zijn! Donderdagavond is er het feestelijke lustrumdiner voor alle leden t.g.v. het 90-jarig bestaan van de NVGE

Vrijdagochtend is er weer casuïstiek en verzorgt de Sectie Gastrointestinale Endoscopie in de Brabantzaal een programma met o.a. een lezing over de 'Richtlijn antistolling'. De Sectie Endoscopie Verpleegkundigen en Assistenten hebben op vrijdagmiddag een eigen programma. Om 12.10 uur zal in de Brabantzaal de uitreiking van de AstraZeneca gastrointestinale Research Award 2003 plaatsvinden. Deze prijs zal uitgereikt worden door de voorzitter van de jury Dr. M.E. Craanen, gevolgd door een erevoordracht van de prijswinnaar. Verder zijn er vrijdag verschillende sessies met vrije voordrachten in de Baroniezaal, de Parkzaal en het Auditorium.

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 2 oktober 2003

DONDERDAG	DIEZEZAAL	BARONIEZAAL	PARKZAAL	AUDITORIUM
12.00-13.00			Vrije voordrachten Nederlandse Vereniging voor Hepatologie p. 7 (let op middagprogramma wordt vervolgd in Auditorium)	
14.00-15.30	Vrije voordrachten Nederlandse Vereniging voor Gastrointestinale Chirurgie p. 7-8	Vrije voordrachten Netherlands Society of Parenteral and Enteral Nutrition p. 9-10	Symposium sectie Maagdarmmotoriek p. 11 *'Gastroesophageale refluxziekte in de praktijk'*	Vrije voordrachten Nederlandse Vereniging voor Hepatologie p. 12-13
15.30-16.00	Theepauze	Theepauze	Vervolg symposium *'Gastroesophageale refluxziekte in de praktijk'*	Theepauze en ledenvergadering
16.00-17.00	Mini-battle: ECRP versus laproscopische choledochus exploratie voor CBD stenen p. 8	Vrije voordrachten Nederlandse Vereniging voor gastroenterologie *Thema's: voeding en mortaliteit* p. 10	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie *Thema's: endoscopie en anorectaal* p. 11-12	Symposium Nederlandse Vereniging voor Hepatologie: NASH p. 13
17.00	'Altana lecture' door Dr. P. de Groen p. 8	Einde programma in deze zaal.	Einde programma in deze zaal.	Vervolg basaal symposium Nederlandse Vereniging voor Hepatologie
17.30	Ledenvergadering NVGE	-	-	-
18.00	Congresborrel, gevolgd door feestavond in de Brabantzaal (aanvang 19.30 uur)	-	-	-

Programma vrijdag 3 oktober 2003

VRIJDAG	BRABANTZAAL	BARONIEZAAL	PARKZAAL	AUDITORIUM
08.30	Casuïstiek voor de klinikus, vrije voordrachten en lezing 'Hemostase en endoscopie' (richtlijn) p. 14	-	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie *Thema: oncologie* p. 17-18 Aanvang 09.00	Vrije voordrachten Nederlandse Vereniging voor Hepatologie p. 19-20
10.00	Sectie Gastrointestinale Endoscopie p. 14-15	Vrije voordrachten Sectie Experimentele Gastro-enterologie/ZONMW Darmfunctie p. 16	Vervolg vrije voordrachten Nederlandse Vereniging voor Gastroenterologie *Thema: IBD en darminfecties*	Vervolg Nederlandse Vereniging voor Hepatologie
11.00	Koffiepauze	Koffiepauze	Koffiepauze	Koffiepauze
11.30	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie p. 15 Uitreiking AstraZeneca Gastrointestinale Research Award 2003 p. 15	International teaching session on Barrett's mucosa p. 17	Geen programma in deze zaal i.v.m. prijsuitreiking in de Brabantzaal	Vervolg Nederlandse Vereniging voor Hepatologie
12.30	Lunchbuffet in expositiehal	Lunchbuffet in expositiehal	Lunchbuffet in expositiehal	Lunchbuffet in expositiehal
14.00	Programma Sectie Endoscopie Verpleegkundigen en Assistenten p. 23	Vrije voordrachten Sectie Experimentele Gastro-enterologie p. 20-21	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie p. 21-22	Geen programma in deze zaal
16.00	Theepauze/einde programma	Theepauze/einde programma	Theepauze/einde programma	Theepauze/einde programma

CURSORISCH ONDERWIJS IN MAAG-DARM-LEVERZIEKTEN **AUDITORIUM**
1 en 2 OKTOBER 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 1 oktober 2003

20.30 - 20.50 uur	Klinische relevantie van 25 jaar gal-onderzoek *Prof. dr. R.P.J. Oude Elferink, Levercentrum, AMC*
21.00 - 21.20 uur	Genetische leverziekten: wat moet je er van weten? *Dr. R.H.J. Houwen, Kinder-MDL, LUMC*
21.30 – 21.50 uur	NASH: “hoe vet de lever aanvalt” *Dr. R.J. de Knegt, MDL, Erasmus MC*
22.00 - 22.20 uur	Auto-immune hepatitis: nieuwe diagnostiek en therapie *Dr. C.M.J. van Nieuwkerk, MDL, VUMC*

Donderdag 2 oktober 2003

08.00 – 08.20 uur	Hepatitis B/C therapie 2005-2010. Wat komt eraan? *Dr. R.A. de Man, MDL, ErasmusMC*
08.30 – 08.50 uur	Radiodiagnostiek levertumoren: “differentiëren we echt” *Dr. E.J. van der Jagt, Röntgen, AZG*
09.00 – 09.20 uur	Resectie primaire levertumoren *Prof. dr. T.M. van Gulik, Heelkunde, AMC*
09.30 – 09.50 uur	Resectie of ablatie bij metastases in de lever *Dr. J.R.M. van der Sijp, Heelkunde, VUMC*

KOFFIE

10.30 – 11.00 uur	Management van eindstadium leverlijden *Prof. dr. F. Nevens, Lever- en Pancreasziekten, Leuven*
11.10 - 11.30 uur	TIPS: niet alleen rondom transplantaties *Prof. dr. J.S. Laméris, Röntgen, AMC*
11.40 - 12.00 uur	Levertransplantatie bij kinderen; worden ze normaal volwassen? *Dr. C.M.A. Bijleveld, Kinder-MDL, AZG*
12.10 – 12.30 uur	Marginale-donor-levers *Dr. J.N.M. IJzermans, Heelkunde, Erasmus MC*

LUNCH

Nederlandse Vereniging voor Hepatologie **Parkzaal**

Voorzitter: R.P.J. Oude Elferink / K.N. Faber

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

12.00 Redirection of PDGF-R targeted adenovirus from hepatocytes to activated stellate cells (p.24)
M.H. Schoemaker, M.G. Rots, L. Beljaars, A.Y. Ypma, P.L.M. Jansen, H.J. Haisma, K. Poelstra and H. Moshage. Center for Liver, Digestive and Metabolic Diseases and Dept of Therapeutic Gene Modulation, University of Groningen.

12.15 Selection of tumor specific promoters for oncolytic adenoviral cholangiocarcinoma gene therapy (p.25).
M. Lie-A-Ling, J.G. Wesseling, R. Hoekstra, T. Deurholt, M.J. Bruno, P.J. Bosma. Dept of Experimental Hepatology, AMC, Amsterdam.

12.30 Development of Lentiviral vectors for cholangiocarcinoma gene therapy (p.26)
M. Lie-A-Ling, J. Seppen, C. Kunne, N. Looije, J. Wesseling, P. Bosma. Dept of Experimental Hepatology, AMC, Amsterdam.

12.45 Reactive oxygen species induce hepatocyte cell death via different mechanisms: a balance between apoptosis and necrosis (p.27).
L. Conde de la Rosa, M. Schoemaker, M. Homan, P.L.M. Jansen and H. Moshage. Dept of Gastroenterology and Hepatology, University Hospital Groningen.

13.00 Lunch

Nederlandse Vereniging voor Gastrointestinale Chirurgie **Diezezaal**

13.30 Inschrijving, koffie

Voorzitters: E.H. Eddes / E.J. Mulder

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

14.00 Genetic alterations in Barrett related adenocarcinomas: a search for early tumor markers (p.28).
L.B. Koppert[1,2], H.W.P.C. van de Meerendonk[2], H. van Dekken[2], H.W. Tilanus[1] and WNM Dinjens[2]. Depts of Surgery[1], Pathology[2], Josephine Nefkens Institute, Erasmus MC, Rotterdam.

14.10 Optimum treatment strategy for early oesophageal adenocarcinoma (p. 29).
M. Westerterp[1], C.J. Buskens[1], P. Fockens[2], F.J.W. ten Kate[3], J.J.B. van Lanschot[1]. Dept of Surgery[1], Dept of Gastroenterology[2], Dept of Pathology[3], Academic Medical Center Amsterdam.

14.20 Laparoscopic versus open total mesorectal excision; a case-control study (p.30).
S.O. Breukink, J.P.E.N. Pierie, C. Hoff, W.J.H.J. Meijerink. Dept of Surgery, Medical Centre Leeuwarden, Leeuwarden.

14.30 Short term results of laparoscopic-assisted versus open restorative (procto-) colectomy: a randomized trial (p.31).
S. Maartense[1], M.S. Dunker[1], J.F. Slors[1], M.A. Cuesta[2], D.J. Gouma[1] and W.A. Bemelman[1]. Dept of Surgery, Academic Medical Center Amsterdam[1] and Dept of Surgery, Free University Medical Center[2], Amsterdam.

14.40 Sentinel node technique for colorectal carcinoma: colon vs rectum (p.32)
A.E. Braat[1], J.W.A. Oosterhuis[1], F.C.P. Moll[2], dr. J.E. de Vries[1]. Dept of Surgery[1] and Pathology[2], Isala clinics location Sophia, Zwolle.

14.50 Lutetium-177 is the most effective radionuclide for radioimmunotherapy of small peritoneal metastases of colorectal origin (p.33).
M.J. Koppe[1], A.C. Soede[2], W.J.G. Oyen[2], O.C. Boerman[2], R.P. Bleichrodt[1]. Depts of Surgery[1] and Nuclear Medicine[2], University Medical Center St Radboud, Nijmegen.

15.00 Prophylactic use of antibiotics in acute (necrotizing) pancreatitis -results of a new meta-analysis- (p.34).
M.G.H. Besselink, V.B. Nieuwenhuijs, M.Th. de Bruijn, L.P. van Minnen, H.G. Gooszen. Dept of Surgery, University Medical Center Utrecht.

15.10 Dynamic graciloplasty in patients born with an anorectal malformation (p.35)
S.M.P. Koch, W. van Gemert, Ö. Uludag, M.J. Rongen, C.G.M.I. Baeten. Dept of Surgery, Academic Hospital Maastricht.

15.20 The return of bowel function after colonic resection (p.36).
R.A. de Roo[1], P.A. Neijenhuis[1], H.M. Schuttevaer[2], R.P. Bleichrodt[3]. Dept of Surgery[1] and Radiology[2] Rijnland Ziekenhuis, Leiderdorp, Dept of Surgery[3] University Medical Centre Nijmegen.

15.30 Theepauze

16.00 **Minibattle NVGIC**
'ERCP versus laparoscopische choledochus exploratie voor CBD stenen'

Gastroenterologie:
Willem Thijs,
Hendrik van Dullemen;

Chirurgie:
Mark van Berge Henegouwen,
Dirk Gouma;

Moderatoren: Bas van Wijnhoven en Pieter Honkoop.

17.00 **Altana Lecture**
Nieuwe toepassingen in de Gastroenterologie (p.37)
Dr. P de Groen (Mayo-clinic, Rochester, U.S.A.)

17.30 Ledenvergadering Nederlands Vereniging voor Gastroenterologie

18.00 Congresborrel expositiehal

19.30 Lustrumdiner Brabantzaal

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

13.30 Ontvangst, inschrijving, koffie

Voorzitters: C.H.C. Dejong / C.F. Jonkers

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

14.00 A closer look at delivered nutrition in the ICU; what you see is not what they get (p.38).
R.J.M. Strack van Schijndel[1], C. Koster[2], A. Bissumbhar[2], G.C.Melis[1]. Nutrition Support team[1], Student[2], VU university Medical Centre, Amsterdam.

14.10 Evaluation of 6 years use of sodium hydroxide solution to clear partially occluded central venous catheters (p.39).
P. Balke[1], S.G. Bader[1], T.A.J. Tas[2], C. F. Jonkers-Schuitema[2], H.P. Sauerwein[2]. University of Amsterdam[1], dept of nutrition and dietetics[2], Nutrition support team, Academic Medical Center, Amsterdam.

14.20 The effect of IGF-I supplemented formula on feeding tolerance and weight gain in preterm infants* (p.40)
D.A.H. de Gast-Bakker[1], J.B. van Goudoever[1], I. van Vliet[1], S.R.D. van der Schoor[1], M. Alles[2], M. Hooijer[2] and D. Tibboel[1]. Sophia Kinderziekenhuis/Erasmus MC[1], Rotterdam, Numico Research[2], Wageningen.

14.30 Plasma glutamine response to enteral and parenteral administration of L-alanyl-L-glutamine in pre-operative patients (p.41)
P.G. Boelens[1], G.C. Melis[1], J.R.M. van der Sijp[1], N.E.P. Deutz[2], P.A.M. van Leeuwen[1]. Dept of Surgery[1], VUMC, Amsterdam and Dept of Surgery[2], University Maastricht.

14.40 Plasma arginine concentrations and de novo arginine production from citrulline are lowered during sepsis (p.42)
Y.C. Luiking[1], M. Poeze[1], L. Steens[2], G. Ramsay[1], N.E.P. Deutz[1]. Depts of Surgery[1] and Intensive Care[2], University Hospital Maastricht and University Maastricht.

14.50 Arginine metabolism in human wounds: acute versus chronic wounds (p.43).
I.B.J.G. Debats[1], N.E.P. Deutz[2], W.D. Boeckx[1], R.R.W.J. v.d. Hulst[1]. Dept of Plastic Surgery[1] and Surgery[2], Academic Hospital Maastricht[1].

15.00 Ornithine pathway is stimulated in human wound healing during Arginine suppletion (p.44).
I.B.J.G. Debats[1], N.E.P. Deutz[2], W.D. Boeckx[1], R.R.W.J. vd Hulst[1]. Dept of Plastic Surgery[1] and Surgery[2], Academic Hospital Maastricht.

15.10 Decreased phenylalanine clearance rate and generalized hyperaminoacidemia following hepatectomy for malignancies in man (p.45).
M.C.G. van de Poll[1], Y.C. Luiking[1], S.J. Wigmore[2], D.N. Redhead[3], O.J. Garden[2], 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, Maastricht University[1], The Netherlands, Surgery[2], Radiology[3], Royal Infirmary, Edinburgh, Scotland.

15.20 Asymmetrical dimethylarginine reflects hepatic function in patients undergoing liver transplantation (p.46).
M.P.C. Siroen[1], M.C. Warlé[2], T. Teerlink[3], R.J. Nijveldt[1], H.W. Tilanus[2], H.J. Metselaar[4], J.R.M. van der Sijp[1], S. Meijer[1], B. van der Hoven[5], P.A.M. van Leeuwen[1]. Depts of Surgery[1] and Clinical Chemistry[3], VU University Medical Center, Amsterdam, and Depts of Surgery[2], Gastroenterology and Hepatology[4], and Surgical Intensive Care Unit[5], Erasmus Medical Center, Rotterdam.

15.30 Theepauze

Nederlandse Vereniging voor Gastroenterologie **Baroniezaal**

Thema's: voeding en motiliteit

Voorzitters: J.B.M.J. Jansen / M. Bruno

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

16.00 Alterations in gene expression profile of the gut due to the starvation (p.47).
M. Sokolovic[1], T.B.M. Hakvoort[1], L.A. Gilhuijs-Pederson[2], D. Wehkamp[2], A.H.C. van Kampen[2], W.H. Lamers[1]. AMC Liver Center[1] and Bioinformatics Laboratory[2], Academic Medical Center, Amsterdam.

16.10 An explorative study on the effect of enzyme supplementation in patients recovered from acute pancreatitis (p.48).
T. Symersky, C.B.H.W. Lamers, A.A.M. Masclee. Dept of Gastroenterology-Hepatology, Leiden University Medical Center.

16.20 Lipid-dependent regulation of transporter gene expression in the small intestine (p.49).
H. van den Bosch, M. Bünger, G. Hooiveld, M. Müller. Nutrition, Metabolism & Genomics group, Wageningen University.

16.30 No indications for imbalance in membrane essential fatty acids (EFA) or altered EFA metabolism in two murine models for cystic fibrosis* (p. 50)
A. Werner[1], M.E.J. Bongers[1], M.J.C. Bijvelds[2], M. Sinaasappel[3], F. Stellaard[1], H.R. de Jonge[2], H.J. Verkade[1]. Pediatric Gastroenterology[1] Academic Hospital, Groningen, Dept Biochemistry[2] and Dept Pediatrics[3], Erasmus University Medical Center, Rotterdam.

16.40 The nutritional gab between ICU and general hospital ward (p.51)
G.C. Melis[1], K.A.C. Berk[2], J.C.M. van der Steen[2], R.J.M. Strack van Schijndel[1]. Nutrition Support Team[1], Student. VU University Medical Centre[2], Amsterdam.

16.50 Excessive belching in aerophagia visualized by oesophageal impedance monitoring: the concept of oesophageal belching (p.52)
B.L.A.M. Weusten[1], J. Silny[2], L.M.A. Akkermans[3], A.J.P.M. Smout[3]. Dept. of Internal Medicine[1], St. Antonius Hospital, Nieuwegein, The Netherlands, Aachen University of Technology[2], FEMU, Aachen, Germany, and Gastrointestinal Motility Unit[3], University Medical Center, Utrecht, The Netherlands.

17.00 Einde programma in deze zaal.
Voor de Altana Lecture kunt u zich begeven naar de Diezezaal.

Sectie Maag Darmmotoriek **Parkzaal**

Symposium
'Gastroesophageale refluxziekte in de praktijk.'

Voorzitters: A.A.M. Masclee / M. Samsom

14.00 Pathogenesse van reflux: blijf bij de LES!
Dr. G.E.E. Boeckxstaens, maag-darm-leverarts., AMC, Amsterdam

14.15 Functie onderzoek bij reflux: meten is wegen?
Dr. M. Samsom, maag-darm-leverarts, UMCU, Utrecht

14.30 Indicaties tot diagnostiek en interventie van reflux bij kinderen
Dr. F. Kneepkens, kinderarts, VUMC, Amsterdam

14.45 Endoscopische behandeling van reflux ziekte
Dr. J. Haringsma, maag-darm-leverarts, Erasmus MC, Rotterdam

15.00 Falen van antireflux endoscopie/chirurgie: waarom en wat nu?
Dr. A.A.M. Masclee, maag-darm-leverarts, LUMC, Leiden

15.15 Discussie

15.30 Einde programma

Nederlandse Vereniging voor Gastroenterologie **Parkzaal**

Thema's: endoscopie en anorectaal

Voorzitters: E.C. Klinkenberg / G.E.E. Boeckxstaens

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

16.00 Efficacy of Activated Recombinant Factor VII (rFVIIa; Novoseven®) in Cirrhotic Patients with Upper Gastrointestinal Bleeding: A Randomized Placebo-controlled Double-blind Multicenter Trial (p.53)
D. Thabut, R. de Franchis, F. Bendtsen, G. d'Amico, A. Albillos, J.G. Abraldes, S. Fabricius, P.C.J. ter Borg[1], H.R. van Buuren[1], J. Bosch, on behalf of a European Study Group. Erasmus Medical Centre[1], Rotterdam.

16.10 Esomeprazole continuous versus on demand maintenance therapy in 1052 gastro-oesophageal reflux disease patients: similar satisfaction but superior quality of life for once daily treatment (p.54)
L.G.J.B. Engels[1], E.C. Klinkenberg-Knol[2], C.P.M. Dekkers[3], J.A. Beker[3], T.G. Tan[3], R.J. Timmerman[3], P.W.E. Haeck[3]. Dept of Gastro-enterology[1], Maasland Hospital, SittardVU Medical Centre[2], Amsterdam, On behalf of the Brilliant study group[3].

16.20 Prospective comparison of hydrogen peroxide-enhanced 3D endoanal ultrasonography, endoanal MR imaging and surgical exploration for perianal fistulas (p.55)
R.L. West[1], D.D.E. Zimmerman[2], S. Dwarkasing[3], S.M. Hussain[3], W.C.J. Hop[4], W.R Schouten[2], E.J. Kuipers[1], R.J.F. Felt-Bersma[1]. Depts of Gastroenterology and Hepatology[1], Surgery[2], Radiology[3], Epidemiology and Biostatistics[4], Erasmus MC University Medical Center Rotterdam.

16.30 Volume measurements of the anal sphincter complex using 3D transanal ultrasonography in incontinent females (p.56)
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.

16.40 Constipation after hysterectomy (p.57)
F.G.M. Timmermans[1], P.P.J. van der Veek[1], P.T.M. Weijenborg[2] and A.A.M. Masclee[1]. Depts of Gastroenterology and Hepatology[1] and Gynecology[2], Leiden Universety Medical Center.

16.50 Cleansing of the colon: comparison of two PEG solutions and a sodium phosphate preparation (p.58)
R.J.F. Felt-Bersma, G. Kooyman, E.J. Kuipers. Dept of Gastroenterology, Erasmus MC, Rotterdam.

17.00 Einde programma in deze zaal.
Voor de Altana Lecture kunt u zich begeven naar de Diezezaal.

Nederlandse Vereniging voor Hepatologie **Auditorium**

Voorzitter: K. J. van Erpecum / J. Seppen

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

14.00 Diosgenin-induced biliary hypersecretion depends on the presence of Abcg8 (p.59)
A. Kosters[1], C. Kunne[1], N. Looije[1], F. Kuipers[2], S. B. Patel[3], A.K. Groen[1]. AMC Liver Center, Academic Medical Center, Amsterdam, The Netherlands[1], Dept of Pediatrics, University Hospital Groningen, Groningen, The Netherlands[2], Div of Endocrinology, Diabetes and Medical Genetics, Medical University of South Carolina, Charleston, SC, USA[3].

14.15 The molecular mechanism of biliary cholesterol secretion (p.60)
A. Kosters[1], C. Kunne[1], N. Looije[1], F. Kuipers[2], S.B. Patel[3], R.P.J. Oude Elferink[1], A.K. Groen[1]. AMC Liver Center, Academic Medical Center, Amsterdam, The Netherlands [1], Dept of Pediatrics, University Hospital Groningen, Groningen, The Netherlands [2], Div of Endocrinology, Diabetes and Medical Genetics, Medical University of South Carolina, Charleston, SC, USA [3].

14.30 FIC1 is expressed at the apical membranes of different epithelial cells in the digestive tract and is induced in the small intestine during postnatal development (p 61)
S.W.C. van Mil[1,2], M.M. van Oort[2], I.E.T. van den Berg[2], R. Berger[2], R.H.J. Houwen[1], L.W.J. Klomp[2]. Dept of Pediatric Gastroenterology[1] and Dept of Metabolic and Endocrine diseases[2], University Medical Center, Utrecht.

14.45 Intestinal bile salt absorption in mice with a mutation in the Fic1 gene (p.62)
A. Groen[1], L. Kuik[1], K. Mok[1], C. Kunne[1], L. Bull[2], L. Agellon[3], W. Kramer[4], C. Paulusma[1], R. Oude Elferink[1]. Lab of Experimental Hepatology, AMC Liver Center, Academic Medical Center, Amsterdam[1], The Netherlands, Liver Center Laboratory, San Francisco General Hospital, University of California, San Francisco[2], California, USA, Dept of Biochemistry, University of Alberta, Edmonton, Alberta[3], Canada, DG metabolic Diseases, Aventis Pharma Deutschland GmbH[4], Germany.

15.00 Highly effective enteral treatment of unconjugated hyperbilirubinemia in Gunn rats* (p.63)
A.M. Hafkamp[1], R. Havinga[1], M. Sinaasappel[2], R.P.J. Oude Elferink[3], H.J. Verkade[1]. Dept Pediatrics, University Hospital Groningen[1], Groningen, Dept. Pediatrics, Erasmus Medical Center[2], Rotterdam; Amsterdam Liver Center, Academic Medical Center[3], Amsterdam.

15.15 Extensive chimerism in liver transplants: vascular endothelium, bile duct epithelium and hepatocytes (p.64)
W.R. ten Hove[1], B. van Hoek[1], I.M. Bajema[2], J. Ringers[3], J.H.J.M. van Krieken[4], E.L. Lagaaij[2]. Dept of Gastroenterology and Hepatology[1], Dept of Pathology[2] and Dept of Surgery[3], Leiden University Medical Center, Dept of Pathology[4], University Hospital Nijmegen.

15.30 Theepauze en ledenvergadering NVH

Nederlandse Vereniging voor Hepatologie **Auditorium**

Voorzitter: R.P.J. Oude Elferink

16.00 **Symposium 'Nonalcoholic Steatohepatitis'**

Clinical aspects of fatty liver
Prof. Hans Romijn (UMC Leiden)

Nuclear receptors, lipogenesis and steatosis
Drs. Aldo Grefhorst (AZ Groningen)

Insulin resistance and fatty liver
Dr. Peter Voshol (TNO)

17.30 Einde programma

Vrijdag 3 oktober 2003

Casuïstiek **Brabantzaal**

Voorzitter: W. Hameeteman

08.30 Casuïstiek voor de klinikus

09.10 Einde casuïstische presentaties

Sectie Gastrointestinale Endoscopie **Brabantzaal**

Voorzitter: W. Hameeteman

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

09.10 Intensive screening methods detect early diffuse lesions in hereditary diffuse gastric cancer (HDGC) (p.65)
J.H.F.M de Bruin[1], F.M. Nagengast[2], J. Bonenkamp[3], J.H.J.M. van Krieken[1]. Dept of Pathology[1], Gastroenterology[2] and Surgery[3]. University Medical Centre St. Radboud, Nijmegen.

09.20 Clinical application of video capsule endoscopy in 70 consecutive patients (p.66)
S.A.C. van Tuyl[1], M.F.J. Stolk[1], R. Timmer[1], E.J. Kuipers[2]. Depts of Gastroenterology, St. Antonius Hospital Nieuwegein[1] and Erasmus MC University Medical Center Rotterdam[2].

09.30 Lezing 'Hemostase en Endoscopie: conceptrichtlijn.'

10.00 Narrow-band imaging improves mucosal pattern recognition in Barrett's oesophagus (p.67)
M. Kara[1], M. Ennahachi[1], F. Ten Kate[2], P. Fockens[1], S. Van Deventer[1], J. Bergman[1]. Dept of Gastroenterology and Hepatology[1], Dept of Pathology[2], Academic Medical Center, Amsterdam.

10.10 A randomized cross-over study comparing Light-induced Fluorescence Endoscopy LIFE) with Standard Video-Endoscopy SE) for detection of early neoplasia in Barrett's Esophagus (BE) (p.68)
M. Kara, W. Rosmolen, M. Smits, P. Fockens, G. Tytgat, J. Bergman. Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam.

10.20 Endoscopic mucosal resection (emr) for high-grade dysplasia (hgd) or early cancer (ec) in Barrett's esophagus (be) (p.69)
J. Bergman[1], F. Peters[1], W. Rosmolen[1], B. Bultje[2], P. Fockens[1], J. van Lanschot[3], F. ten Kate[4], S. van Deventer[1], G. Tytgat[1]. Depts. of Gastroenterology[1], Clinical Epidemiology and Biostatistics[2], Surgery[3], Pathology[4], Academic Medical Center, Amsterdam.

10.30 5-Aminolevulinic Acid Photodynamic Therapy versus Argon Plasma Coagulation for Ablation of Barrett's Esophagus: A Randomized Trial (p.70)
M. Hage[1,2], P.D.Siersema[1], H. van Dekken[2], E.W. Steyerberg[3], J. Haringsma[1], W. v.d. Vrie[1], T.E Grool[1], R.L.P. van Veen[4], H.J.C.M. Sterenborg[4], E.J. Kuipers[1]. Depts of Gastroenterology & Hepatology[1], Pathology[2], Public Health[3] and Radiation Oncology (Photodynamic Therapy and Optical Spectroscopy Programme)[4] Erasmus MC University Medical Center Rotterdam.

10.40 Self-expanding metal stents with anti-reflux valve for the prevention of gastroesophageal reflux: a randomized trial (p.71)
M.Y.V. Homs[1], P.J. Wahab[2], E.W. Steyerberg[3], J. Haringsma[1], T.A. Grool[1], E.J. Kuipers[1], P.D. Siersema[1]. Dept. of Gastroenterology & Hepatology[1] and Public Health[3], Erasmus MC / University Medical Center Rotterdam, Dept. of Gastroenterology[2], Rijnstate Hospital Arnhem.

10.50 Good palliation with Self-Expanding Metal Stents (SEMS) for malignant obstruction of the colon: a five-years experience (p.72)
R.J.I. Bosker[1], F. ter Borg[2], E.H. Eddes[1], M.M.J.J.R. Jaspers[3], M. Eeftinck Schattenkerk[1]. Dept. of Surgery[1], Gastroenterology[2] and Radiology[3], Deventer Hospital.

11.00 Koffiepauze

Nederlandse Vereniging voor Gastroenterologie **Brabantzaal**

Voorzitter: G.P. van Berge Henegouwen

Voordrachten in het Nederlands, spreektijd 10 of 15 minuten incl. discussie van resp. 3 en 5 min.

11.30 Presentatie MLDS voordracht, 'Genetische factoren bij anusatresie' (p.73)
Prof. dr. H.G. Brunner, Universitair Medisch Centrum St. Radboud, Nijmegen

11.40 High homocysteine levels, and not vitamin B12 deficiency, increase the risk of ischemic relapse and mortality (p.74)
F. Vlemmix, M.G.H. van Oijen, R.J.F. Laheij PhD, L. Paloheimo, J.B.M.J. Jansen MD PhD, F.W.A. Verheugt MD PhD. Dept of Gastroenterology and Cardiology, UMC St Radboud, Nijmegen.

11.55 LapBand vs. open VBG, a prospective randomized trial (p.75)
F.M.H. van Dielen[1], P.B. Soeters[1], G.A.P.G. van Mastrigt[2], J.W.M. Greve[1]. Dept of General Surgery[1], Dept of Clinical Epidemiology and Medical Technology Assessment[2], university hospital of Maastricht.

12.10 **AstraZeneca Gastrointestinale Research Award 2003,**
uitreiking door de voorzitter van de jury Dr. M.E. Craanen, gevolgd door erevoordracht door de prijswinnaar

12.30 Lunchbuffet in de expositiehal

Sectie Experimentele Gastroenterologie/ZONMW Darmfunctie **Baroniezaal**

Voorzitter: M.A.C. Meijssen / H.W. Verspaget

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

10.00 The cholinergic anti inflammatory pathway regulates host defense during septic peritonitis in mice (p.76)
D.J. van Westerloo[1], J. Winkelhagen[2], J. Daalhuisen[1], M.J. Bruno[3], K.J. Tracey[4], A.F. de Vos[1], S. Florquin[5] and T. van der Poll[1]. Depts of Experimental Internal Medicine[1], Surgery[2], Gastroenterology[3] and Pathology[5], AMC Amsterdam, The Netherlands. Lab of biomedical sciences[4], North shore Long Island Jewish Research Institute, NY, USA.

10.10 Versatile roles for Bone Morphogenetic Protein in gut development and gastric cancer (p.77)
S.A. Bleuming, G.R. van den Brink[1], S.J.H. van Deventer[2], M.P. Peppelenbosch[1]. Dept of Experimental Internal Medicine[1], and Dept of Gastroenterology[2], Amsterdam Medical Center, Amsterdam.

10.20 Nickel-responsive induction of urease activity is restricted to gastric Helicobacter species (p.78)
A.H.M. van Vliet, J. Stoof, E.J. Kuipers and J.G Kusters, Erasmus MC, Rotterdam.

10.30 Detection of high-level tetracycline resistance in Helicobacter pylori using PCR-RFLP (p.79)
M.M. Gerrits[1], M.L. Ribeiro[2], M. Berning[1], E.J. Kuipers[1], S. Mendonça[2], A.H.M. van Vliet[1], J. Pedrazzoli Jr.[2] and J.G. Kusters[1]. Dept of Gastroenterology and Hepatology[1], Erasmus MC-University Medical Center Rotterdam, The Netherlands, Clinical Pharmacology and Gastroenterology Unit[2], São Francisco University Medical School, Bragança Paulista, SP, Brazil.

10.40 B-cells produce immunoregulatory molecules in both HLA-B27 rats with colitis and non-transgenic littermates (p.80)
F. Hoentjen[1,2], S.L. Tonkonogy[3], R. Balfour Sartor[2], C.J. Mulder[1] and L.A. Dieleman[2]. Dept of Gastroenterology[1], Vrije Universiteit Amsterdam, The Netherlands, Center for Gastrointestinal Biology and Disease[2], University of North Carolina at Chapel Hill, Chapel Hill, USA,College of Veterinary Medicine[3], NC State University, Raleigh, USA.

10.50 In vitro intestinal intercellular adhesion molecule-1 (ICAM-1, CD54) expression is decreased by the n-3 PUFA eicosapentaenoic acid (EPA) (p.81)
J.D. Ramakers, R.P. Mensink J. Plat. Dept of Human Biology, Maastricht University, Nutrition and Toxicology Research Institute Maastricht.

11.00 Koffiepauze

Sectie Experimentele Gastroenterologie **Baroniezaal**

International Teaching Session on Barrett's mucosa

Voorzitters: J.G. Kusters / H. Verspaget

11.30 Barrett's mucosa – A pathologist's view
Dr. M. Vieth, Institute of Pathology, Otto-von-Guericke University Magdeburg, Germany

12.00 Barrett's mucosa – A clinician's view
Dr. J. Jankowski, University Department of Cancer Studies and Molecular Medicine, Leicester University Hospitals, Leicester, United Kingdom

12.30 Lunchbuffet in de expositiehal

Nederlandse Vereniging voor Gastroenterologie **Parkzaal**

Thema: oncologie

Voorzitter: H. Boot / A. Cats

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

09.00 Cost study of high dose rate brachytherapy and stent placement in the palliation of dysphagia due to cancer of the esophagus and esophagogastric junction (p.82)
S. Polinder, M.Y.V. Homs, P.D. Siersema, E.W. Steyerberg for the Dutch SIREC study group. Erasmus MC/University Medical Center Rotterdam.

09.10 Limited transhiatal versus extended transthoracic resection for adenocarcinoma of the distal esophagus or cardia (p.83)
J.B.F. Hulscher[1], J.W. van Sandick[1], A.G.E.M. de Boer[2], B.P.L.Wijnhoven[3], J.G.P. Tijssen[4], P. Fockens[5], P.F.M. Stalmeier[2], F.J.W. ten Kate[6], Van Dekken[7], H. Obertop[1], J.J.B. van Lanschot[1]. Depts of Surgery[1], Medical Psychology[2], Cardiology[4], Gastroenterology[5] en Pathology[6], Academisch Medisch Centrum Amsterdam, Depts of Surgery[3] en Pathology[7], Erasmus Medisch Centrum Rotterdam.

09.20 The predictive value of alarm symptoms for upper gastrointestinal malignancies: results of a meta-analysis (p.84)
G.A.J. Fransen[1], J.W.M. Muris[1], R.J.F. Laheij[2]. Dept of General Practice[1], University of Maastricht, Maastricht and Dept of Gastroenterology[2], UMCN St. Radboud, Nijmegen.

09.30 Effects of naturally occurring dietary anticarcinogens and nonsteroidal anti-inflammatory drugs on rat hepatic and intestinal UDP-glucuronosyltransferases (p.85)
E.M.J. van der Logt, H.M.J. Roelofs, E.M.M. van Lieshout, F.M. Nagengast and W.H.M. Peters. Dept of Gastroenterology, University Medical Centre St Radboud, Nijmegen.

09.40 Oral calcium intake after first colonic polipectomy does not reduce polyp recurrence rate, a five years randomised clinical trial (p.86)
E.T.P. Keulen, T.A.F. Engels, H.M.J.M. Verhoeven, L.P. Bos, L.G.J.B. Engels. Dept of Internal Medicine and Gastro-Enterology, Maasland Hospital Sittard-Geleen.

09.50 Peripheral Blood Phenotyping in (Refractory) Coeliac Disease as a Marker of Pre-Malignancy? (p.87)
M.S. Goerres[1], C.J.J. Mulder[2], P.J. Wahab[1], J.A.M. Kerckhaert[3], H. van Dijk[4]. Dept of Gastroenterology[1] Rijnstate Hospital, Arnhem and Gastroenterology[2], VU Medical Centre, Amsterdam and Immunology[3], Rijnstate Hospital, Arnhem and Immunology[4] Meander Medical Center, Amersfoort.

10.00 Relationship between the CYP1A2–164A →C polymorphism (CYP1A2*1F) and risk for colorectal neoplasia in humans (p.88)
H.J.J. Moonen[1], L.G.J.B. Engels[2], J.C.S. Kleinjans[1], T.M.C.M. de Kok[1]. Dept of Health Risk Analysis and Toxicology[1], Maastricht University and Dept of Gastroenterology[2], Maasland Hospital, Sittard.

10.10 The yield of colonoscopy and sigmoidoscopy in a young population not at risk for familial colorectal cancer (p.89)
A.E. de Jong[1,2], K.F. Wong[1], H. Morreau[3], H.F.A. Vasen[1,2] & The National Collaborative group on HNPCC and FAP. The Netherlands Foundation for the Detection of Hereditary Tumours[1], Leiden, Dept of Gastroenterology[2], Dept. of Pathology[3], Leiden University Medical Center.

10.20 Prevalence of ileal anal pouch adenomas in patients with familial adenomatous polyposis (p.90)
P. Friederich[1], M. Berkhout[1], J.H.J.M. van Krieken[2], H.M. Vasen[3], F.M. Nagengast[1]. Dept of Gastroenterology[1], UMCN, Nijmegen.

10.30 Comparison of the glutathione S-transferase activity and isoenzym levels in the mucosa of the ileal pouchand afferent loop in familial adenomatous polyposis: possible risk factor for adenoma recurrence (p.91)
P. Friederich[1], M. Berkhout[1], J.H.J.M. van Krieken[2], W.H.M. Peters[1], F.M. Nagengast[1]. Depts of Gastroenterology and Hepatology[1] and Pathology[2], University Medical Centre St. Radboud, Nijmegen.

10.40 Diagnostic accuracy of CT colonoscopy with intravenous contrast and without colonic cleansing versus conventional colonoscopy for the detection of colorectal polyps (p.92)
J.M. Jansen[1], M.H.J. Voormolen[2], K.H. Schuur[2], W.N.H.M. Stuifbergen[1], A.W.M. Van Milligen de Wit[1]. Dept of Internal Medicine and Gastroenterology[1], Radiology[2], St. Elisabeth Hospital, Tilburg.

10.50 Malignant colorectal polyps: is endoscopic resection and follow-up a safe strategy? (p.93)
F. ter Borg[1], A. Aslan[1], M. Ledeboer[1], J.W. Arends[2], M. Eeftinck Schattenkerk[3], E.H. Eddes[3]. Depts of Gastroenterology[1], Pathology[2] and Surgery[3], Deventer Hospital.

11.00 Koffiepauze, einde programma in deze zaal.

Nederlandse Vereniging voor Hepatologie **Auditorium**

Voorzitters: P.L.M Jansen / R.J. de Knegt

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

09.00 Response to alpha-interferon prolongs survival and reduces the risk of hepatocellular carcinoma in chronic hepatitis B (p.94)
M. van Zonneveld[1], H.G.M. Niesters[2], R.A. de Man[1], S.W. Schalm[1], H.L.A. Janssen[1]. Depts of Gastroenterology and Hepatology[1] and Virology[2], Erasmus Medical Center Rotterdam.

09.15 Hepatitis B virus genotypes in HBeAg-positive patients: geographic distribution and relation to viral replication and fibrosis (p.95)
J.T. Sarneel[1], H.G.M. Niesters[2], R.A. de Man[1], S.W. Schalm[1], H.L.A. Janssen[1]. Dept of Gastroenterology and Hepatology[1], Dept of Virology[2], Erasmus Medical Centre, Rotterdam.

09.30 Combined cytolytic and noncytolytic intrahepatic CD8 T-lymphocyte reactivity is important for response to antiviral therapy in chronic hepatitis B patients (p.96)
T.J. Tang, J. Kwekkeboom, S. Mancham, R.S. Binda, J.G. Kusters, S.W. Schalm, H.L.A. Janssen. Dept of Gastroenterology and Hepatology, Erasmus MC, Rotterdam.

09.45 Recipient CTLA-4 +49 G/G genotype is associated with reduced incidence of acute rejection after liver transplantation (p.97)
J. Kwekkeboom[1], Ph. de Reuver[2], V. Pravica[4], W. Hop[3], P. Boor[1], H.J. Metselaar[1], I.V. Hutchinson[4], H.W. Tilanus[2]. Depts of Gastroenterology and Hepatology[1], Surgery[2] and Epidemiology and Biostatistics[3], Erasmus Medical Center, Rotterdam, The Netherlands and Immunology Research Group[4], School of Biological Sciences, University of Manchester, UK.

Voorzitters: H.L.A. Janssen / R.J. de Knegt

10.00 Long term follow-up of interferon non-responders with chronic hepatitis C: Effect of glycyrrhizin on HCC development (p.98)
B.E. Hansen[1,2], K. Ikeda[3], B.J. Veldt[2], E. Verheij[2], H. Suzuki[4], S.W. Schalm[2]. Dept of Epidemiology and Biostatistics[1], Erasmus Medical Center, Rotterdam, The Netherlands. Dept of Gastroenterology and Hepatology[2], Erasmus Medical Center, Rotterdam The Netherlands. Dept of Gastroenterology[3], Toranomon Hospital, Tokyo, Japan. Yamanashi Medical University[4], Yamanashi, Japan.

10.15 Long term follow up of sustained responders to interferon alpha in chronic hepatitis C: A meta-analysis assessing true clinical endpoints (p.99)
B.J. Veldt[1], G. Saracco[2], B.E. Hansen[3], S.W. Schalm[1]. For the Eurohep* study group. Dept of Gastroenterology and Hepatology[1], Erasmus Medical Center, Rotterdam, The Netherlands, Dept of Gastroenterology[2], Ospedale Molinette, Torino, Italy, Dept of Epidemiology and Biostatistics[3], Erasmus Medical Center, Rotterdam, The Netherlands, *Eurohep study group participants are U. Hopf, Berlin; N. Boyer, Clichy; O. Weiland, Huddinge; F. Nevens, Leuven; I. Castillo, Madrid; A. Bellobuono, Milan; C. Cammà and A. Craxi, Palermo; P. Marcellin, Paris; S.W.Schalm and J.T. Brouwer, Rotterdam and G.Saracco, Torino.

10.30 Distinct intrahepatic immunological environment in chronic viral hepatitis analysed by flow cytometry of Fine-Needle-Aspiration-Biopsies (p.100)
D. Sprengers, R.G. van der Molen, J. Kusters, J. Kwekkeboom, L.J.W. van der Laan, S.W. Schalm, H.L.A. Janssen. Dept Gastroenterology and Hepatology, Erasmus MC, Rotterdam.

10.45 Development of a novel, accurate and flexible limited sampling method for ciclosporin monitoring after liver transplantation avoids possible overdosing with trough level monitoring and underdosing with 2-hour monitoring (p.101)
P. Langers, M.S.[1], S. Cremers, Ph.D.[2], J. den Hartigh, Ph.D.[2], R. Veenendaal, M.D.,Ph.D.[1], R. ten Hove, M.D.[1], J. Ringers, M.D.[3], C.B.H.W. Lamers, M.D., Ph.D.[1], B. van Hoek, M.D., Ph.D.[1]. Dept of Gastroenterology and Hepatology[1], Dept of Clinical Pharmacology[2] and Dept of Surgery[3], Leiden University Medical Center, Leiden.

11.00 Koffiepauze

11.30 Follow up of Epstein Barr virus polymerase chain reaction after liver transplantation in pediatric patients (p. 102)
R. Scheenstra[1], E.A.M. Verschuren[2], S.J.C. Stevens[3], T.H. The[2], H.J. Verkade[1], C.M.A. Bijleveld[1]. Dept of Pediatric Gastro-enterology[1] and Clinical Immunology[2], Academical Hospital Groningen, Dept of Pathology[3], Free University, Amsterdam.

11.45 Prevalence of other diseases in patients with primary biliary cirrhosis (PBC) (p.103+104). P.C.J. ter Borg[1], H.R. van Buuren[1], K.M.J. van Nieuwkerk[2], E.B. Haagsma[3], J.W. den Ouden[4], M.H.M.G. Houben[5], R.W. de Koning[6], E.W. van der Hoek[7], R. Adang[8], G.P. van Berge Henegouwen[9] for the Dutch Multicenter PBC study group. Dept of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam[1], Dept of Gastroenterology and Hepatology, VU Hospital, Amsterdam[2], Dept of Internal Medicine, University Hospital Groningen[3], Dept of Internal Medicine, St. Franciscus Hospital, Rotterdam[4], Dept of Internal Medicine, Rode Kruis Hospital, Den Haag[5], Dept of Internal Medicine, Canisius Hospital, Nijmegen[6], Dept of Internal Medicine, Carolus Hospital, Den Bosch[7], Dept of Internal Medicine, VieCuri MC, Venlo[8], Dept of Gastroenterology and Hepatology, University Medical Center Utrecht[9].

12.00 Einde programma in deze zaal.

Sectie Experimentele Gastroenterologie **Baroniezaal**

Voorzitters: M.A.C. Meijssen / J.G. Kusters

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

13.30 Ledenvergadering Sectie Experimentele Gastroenterologie

14.00 Increased mucosal expression of Matrix Metallo Proteinases-2 and –9 in inflammatory bowel disease and the prognostic impact for relapse in Crohn's disease (p.105). M.J.W. Meijer[1], W. van Duijn[1], M.A.C. Mieremet-Ooms[1], J.M. van der Zon[1], G Kuiper[1], R.A. van Hogezand[1], R. Hanemaaijer[2], J.H. Verheijen[2], C.B.H.W. Lamers[1], H.W. Verspaget[1]. Dept of Gastroenterology-Hepatology, Leiden University Medical Center, Leiden[1], Gaubius Laboratory, TNO-PG, Leiden[2].

14.10 A functional single nucleotide polymorphism of the TLR4 gene is correlated with Crohn's disease and not with ulcerative colitis (p.106)
H. Braat[1], M. Dijkgraaf[2], W. Curvers[1], E. Vogels[1], A. van Bodegraven[3], P. Stokkers[4], D. Hommes[4], S. van Deventer[4]. Dept of Experimental Internal Medicine[1], Dept of Biostatistics [2], Dept Gastro-intestinal Disease VUMC [3] and Dept of Gastro-intestinal Disease AMC [4], Academic Medical Center, Amsterdam.

14.20 Reciprocal regulation of HO-1 and iNOS in intestinal epithelial cells in response to oxidative stress (p.107)
G. Dijkstra, H. Blokzijl, L. Bok, M. Homan, P.L.M. Jansen, H. Moshage. University Hospital, dept of Gastroenterology and Hepatology, Groningen.

14.30 Inhibition of cyclooxygenase activity reduces rotavirus infection* (p.108)
J.W.A. Rossen, J. Bouma, H.C. Raatgeep, H.A. Büller and A.W.C. Einerhand. Lab of Pediatrics, Erasmus MC - Sophia Rotterdam.

14.40 Celecoxib directly interferes with the Wnt pathway independent of Cox-2 in colon cancer (p.109)
J.B.Tuynman, R.van der Neut, M.P. Peppelenbosch, D.J. Richel. Academisch Medisch Centrum, Amsterdam.

14.50 Mesalazine acts directly on the Wnt/APC/beta-catenin pathway via protein phosphatase 2A (p.110)
C.L. Bos[1,2], M.P. Peppelenbosch[2], J.C.H. Hardwick[3], D.J. Richel[1]. Dept of Medical Oncology[1] and Experimental Internal Medicine[2] and Gastroenterology[3], Academic Medical Center, Amsterdam.

15.00 Einde programma.

Nederlandse Vereniging voor Gastroenterologie **Parkzaal**

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thema: IBD en darminfecties

Voorzitters: S.D.J. van der Werf / A.A. van Bodegraven

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

14.00 Dynamic MRI of Gastric Motility and Emptying: Response to Somatostatin in Healthy Subjects (p.111)
I.M. de Zwart, A. de Roos, H.J. Lamb, P. Kunz, A.A.M. Masclee., Leiden University, Medical Center, Dept. of Radiology and Gastroenterology.

14.10 A comparison of azathioprine-induced pancreatitis in Crohn's disease versus other diseases (p.112)
R.K. Weersma[1], F.T.M. Peters[2], L.E. Oostenbrug[2], A.P. van den Berg[2], R.J. Ploeg[3], M. van Haastert[4], H.M. van Dullemen[5]. Dept of Gastroenterology and Hepatology[1], Medisch Spectrum Twente, Enschede, dept of Gastroenterology and Hepatology [2], dept of Surgery[3], University Hospital, Groningen, dept of Gastroenterology and Hepatology[4], Martini Hospital, Groningen.

14.20 Maintenance treatment with Budesonide 6mg versus 9mg once daily in patients with Crohn's disease in remission (p.113)
D.J. de Jong[1], D.J. Bac[2], T.G. Tan[3], S.Y. de Boer[4], J.B.M.J. Jansen[1], T. Hoofwijk[5], R. Müller[6], A.H.J. Naber[1]. Dept of Gastroenterology, University Medical Centre Nijmegen[1], Ikazia Hospital Rotterdam[2], Hospital Midden Twente Hengelo[3], Slingeland Hospital Doetinchem[4], Tramedico International BV Weesp[5], The Netherlands, Dr. Falk Pharma GmbH Freiburg[6], Germany.

14.30 Intravenous Pamidronate in Combination with Calcium and Vitamin D Is Highly Effective for Treatment of Low Bone Mineral Density in Crohn's Disease (p.114)
P. Stokkers[1], T. Schreuder[2], M. Deley[1], M. van der Spek[1], S. van Deventer[1], C. Mulder[2], D. Hommes[1]. Academisch Medisch Centrum[1], Amsterdam, Rijnstate Ziekenhuis[2], Arnhem.

14.40 Probiotics (VSL#3) in Arthralgia. Preliminary results of an ongoing open trial in patients with ulcerative colitis and Crohn's disease (p.115)
O. Karimi, A.S. Peña, A.A. van Bodegraven. Dept of Gastroenterology and Lab of Immuno-genetics, VUmc, Amsterdam.

14.50 Dietary calcium inhibits diarrhea due to enterotoxigenic Escherichia coli infection in humans (p.116)
I. Bovee-Oudenhoven[1], M. Lettink-Wissink[1], W. van Doesburg[1], B. Witteman[2] and R. van der Meer[1]. WCFS/NIZO food research[1] and Gelderse Vallei Hospital[2], Ede.

15.00 ORS with a mixture of non-digestible carbohydrates in the treatment od acute diarrhea: a randomised placebo controlled study by the ESPGHAN Working Group on Intestinal Infections* (p.117)
J.H. Hoekstra[1], H. Szajewska[2], M. Abu Zikri[3], D. Micetic-Turk[4], Z. Weizman[5], A. Papadopoulou[6], A. Guarino[7], J.A. Dias[8], B. Oostvogels[1]. Hieronymus Bosch Hospital[1], 's-Hertogenbosch, Dept Pediatric Gast[2], Warsaw, Children's Hospital[3], Cairo, Maribor Teaching Hospital[4], Dept Pediatrics[5], Beer Sheva, Children's Hospital Athens[6], Dept Pediatrics Naples[7], Facultado de Medicine Porto[8] .

15.10 Gastric acid-suppressive therapy and community-acquired respiratory infections (p.118) R.J.F. Laheij, M.C. van IJzendoorn, M.J.R. Janssen, J.B.M.J. Jansen. Dept of Gastroenterology, University Medical Center St Radboud, Nijmegen.

15,20 Effect of black tea in an ex vivo model of infectious diarrhoea in piglet small intestine (p.119) M.J. Bruins[1], J. van der Meulen[2], J.M.M. van Amelsvoort[1], B.J.W. van Klinken[1]. Unilever Health Institute[1], Unilever R&D Vlaardingen and Institute for Animal Science and Health[2], ID-Lelystad.

15.30 Validation of a new portable near patient urea breath test; the Heliprobe system (p.120). W.A. de Boer[1], C. Van Alfen[1], S. Badrawi[1], A.H.A.M. Van Oijen[1], J.B.M.J. Jansen, J. Rydén[2]. Dept of Internal Medicine[1], Ziekenhuis Bernhoven, Oss, Netherlands, Noster System AB[2], Stockholm, Sweden.

15.40 A prospective comparison between Magnetic Resonance Cholangiopancreatography and Endoscopic Ultrasonography for the detection of common bile duct stones (p.121). J.E. van Hooft[1], F. ter Borg[1], R.M.M.J.J.R. Jaspers[2], M. Ledeboer[1]. Dept of Gastroenterology[1] and Radiology[2], Deventer Hospital.

15.50 When should we perform an ERCP in the setting of an acute pancreatitis of suspected biliary origin? (p.122). H. van Cruijsen, C. Buis, F. Jenniskens, F. ter Borg, H.J.A. Hazenberg. Dept of Gastro-enterology, Deventer Hospital.

16.00 Einde programma in deze zaal.

Sectie Endoscopie Verpleegkundigen en Assistenten **Brabantzaal**

13.30 - 14.00	Algemene ledenvergadering SEVA
14.00 - 14.20	Mw. G. Kooijman, verpleegkundige, Erasmus MC, Rotterdam. Lavage van het colon: vergelijkend onderzoek tussen twee peg-preparaten en natriumfosfaat.
14.20 - 14.40	Dr. R.A. de Man, maag-darm-leverarts, Erasmus MC, Rotterdam Resultaten HAV onderzoek onder endoscopie-assistenten.
14.40 - 15.00	Theepauze
15.00 - 15.20	Mw. A. van Willigen, Ikazia ziekenhuis, Rotterdam Rol endoscopieassistent bij het plaatsen van de Peg sonde.
15.20 - 15.40	Mw. E. Ploeger en mw. A. Tijssen, verpleegkundigen OLVG, Amsterdam Ontwerp en ontwikkeling van een moderne endoscopie unit.
15.40- 16.00	Dr. E.A.J. Rauws, maag-darm-leverarts, AMC, Amsterdam Ervaringen met de Gold-probe injectie therapie bij gastro-intestinale bloedingen.
16.00	Einde programma

Redirection of PDGF-R targeted adenovirus from hepatocytes to activated stellate cells

M.H. Schoemaker, M.G. Rots, L. Beljaars, A.Y. Ypma, P.L.M. Jansen, H.J. Haisma , K. Poelstra and H. Moshage. Center for Liver, Digestive and Metabolic Diseases and Dept of Therapeutic Gene Modulation, University of Groningen.

Background: Hepatic stellate cells (HSCs) are the principal producers of excessive extracellular matrix in liver fibrosis. Therefore, HSCs are an attractive target for anti-fibrotic therapy. However, current therapy for liver fibrosis is ineffective and hampered by serious side-effects, due to a lack of current drugs for HSCs. A promising vehicle for delivering therapeutic genes to cells is the adenovirus. Since more than 90% of intravenously administered adenovirus is taken up by hepatocytes and Kupffer cells in the liver, retargeting to HSCs is necessary for efficient gene delivery. Activated HSCs highly express the Platelet Derived Growth Factor Receptor (PDGF-R). Aim: retargeting of adenovirus to activated HSCs using a fusion protein recognizing both the adenovirus and the Platelet Derived Growth Factor-receptor (PDGF-R). Methods: A retargeting construct, composed of a PDGF peptide cloned in front of the single chain antibody fragment directed against the adenovirus knob was expressed in bacteria and purified by affinity-chromatography. A scrambled version of the PDGF peptide was used as negative control. Adenoviral retargeting was tested using culture-activated rat stellate cells, 3T3/NIH fibroblasts and primary cultured rat hepatocytes. Cellular expression of transduced genes was determined by expression of luciferase activity. Results: Both 3T3 fibroblasts and activated rat stellate cells showed enhanced gene transfer by the PDGF-R-retargeted adenovirus. The single chain antibody fragment alone or the scrambled fusion protein did not result in uptake of adenovirus. PDGF-R-retargeted adenovirus showed markedly decreased tropism for hepatocytes compared to wildtype or control adenoviruses. Conclusion: Succesful retargeting of adenovirus from hepatocytes to activated stellate cells was achieved using PDFG-R-retargeted adenovirus. This re-targeted adenovirus can now be applied to direct therapeutic genes to stellate cells as treatment for liver fibrosis.

Selection of tumor specific promoters for oncolytic adenoviral cholangiocarcinoma gene therapy

M. Lie-A-Ling, J.G. Wesseling, R. Hoekstra, T. Deurholt, M.J. Bruno, P.J. Bosma. Dept of experimental Hepatology, AMC, Amsterdam.

The inherent compartmentalization in the biliary system makes cholangiocarcinoma an attractive target for gene therapy especially since current treatment modalities are ineffective. Gene therapy trials using replication deficient adenoviral vectors show that this approach is safe but, due to limited penetration, lacks efficacy. To overcome this, replicating adenoviral vectors are being developed.
Due to the hepatotropism of adenoviral vectors, it seems essential to limit the replication to the tumor especially for tumors localized in the liver like CC. This specific replication can be achieved by using tumor/-tissue specific promoters (TSP) to control adenoviral replication. For CC the ideal TSP should have high expression in this cancer and very low expression in hepatocytes. Based on their association with CC we selected 5 candidate promoters: cyclooxygenase-2, midkine, human telomerase reverse transcriptase (hTERT) and mucin 1(DF3). In addition we chose the promoter of Cytokeratin 19 (CK19). The expression of this epithelial marker persists in transformed cells while heaptocytes do no express this protein. We produced 8 replication deficient luciferase (LUC) expressing adenoviral vectors spanning all selected TSPs. LUC activity was determined in 4 human CC cell lines, primary human hepatocytes and primary cholangiocytes. To eliminate the large differences in transduction efficiency between different cell lines and primary cells, we normalized the luciferase expression to the number of viral genomes present in the cells. This normalization showed that reference promoters like CMV and SV-40 commonly used to compare promoter strength are differently expressed in the cell lines tested. CK19, hTERT and DF3 promoters were found to have the best “tumor on hepatocyte off” characteristics and will be tested in primary human CC biopsy material and for the generation of replication competent adenoviral vectors.

Development of Lentiviral vectors for cholangiocarcinoma gene therapy

M. Lie-A-Ling, J. Seppen, C. Kunne, N. Looije, J. Wesseling, P. Bosma.
Dept of Experimental Hepatology, AMC, Amsterdam.

Limited treatment options for cholangiocarcinoma (CC) and the inherent compartmentalization in the biliary system make it an attractive target for gene therapy. Drawbacks of the adenoviral gene therapy are transient gene expression and it's immunogenicity. Since HIV based lentiviral vectors result in a permanent expression of transgenes and have low immunogenicity, we investigated if these vectors are effective for CC gene therapy. First we compared the transduction of both vectors in several human cholangiocarcinoma cell lines and showed that lentiviral transduction efficiency is comparable to adenovirus. Next we assessed the potential of lentivirus as a vector for cytotoxic cancer gene therapy by cloning cytosine deaminase (CD) in both viral vectors. CD converts the pro-drug 5-fluorocytosine into the chemotherapeutic 5-fluorouracil. To be able to identify the transduced cells both vectors also expressed GFP. Adenoviral transduction of 10% of the cholangiocarcinoma cells resulted in efficient cell kill upon the addition of 0,6 mM 5-FC. In contrast, lentiviral transduction of 50% of the cells still showed no efficient cell kill. Only when using an excess of lentiviral vector resulting in 100% transduction was cell kill observed, indicating that CD is expressed and does work. This difference in efficacy was unexpected since both vectors contain identical constructs. We are currently investigating whether these differences are due to lower expression levels of lentiviral vectors or if presence of adenoviral proteins makes cells more susceptible to chemotherapy. These results show that cytotoxic approach does not seem to be feasible with lentiviral vectors. Currently we are testing the effect of a secreted fusion protein of the amino terminal fragment of the urokinase plasminogen activator and the bovine pancreas trypsin inhibitor that blocks pericellular proteolysis and may be able to inhibit tumor neoangiogenisis and invasion.

Reactive oxygen species induce hepatocyte cell death via different mechanisms: a balance between apoptosis and necrosis

L. Conde de la Rosa , M. Schoemaker, M. Homan, P.L.M. Jansen and H. Moshage. Dept Gastroenterology and Hepatology, University Hospital Groningen.

Background: Liver injury in many liver diseases is caused by death of hepatocytes. Cell death can follow two pathways, apoptosis or necrosis. Different reactive oxygen species, e.g. superoxide anion and hydrogen peroxide (H2O2), are increased in liver diseases and may induce cell death via different mechanisms. It is important to know these mechanisms because blocking cell death may prevent liver injury. Aim: To compare the mechanisms of hepatocyte death induced by superoxide anions and H2O2. Methods: Hepatocytes were exposed to the superoxide anion donor menadione or H2O2. Survival pathways were manipulated using dominant negative FADD, and inhibitors of p38 and ERK MAPK, protein kinase C and PI-3-kinase, nitric oxide donor and caspase-8 inhibitor. H2O2 detoxification was inhibited using the catalase inhibitor 3-aminotriazole. Apoptosis was determined by measuring caspase-3 activity and necrosis by Sytox Green staining. Results: Superoxide anion induces apoptosis, but not necrosis. Superoxide anion-induced apoptosis is FADD-independent, but caspase-8-dependent and prevented by superoxide dismutase mimic MnTBAP and by reduced GSH. H2O2 does not induce cell death. Inhibition of survival pathways did not increase H2O2 toxicity, but inhibition of catalase induces necrosis. Superoxide anion-induced cell death is switched to necrosis by nitric oxide due to peroxynitrite formation and by shifting superoxide anion metabolism to H2O2 by MnTBAP and catalase inhibition. Conclusion: Distinct ROS induce cell death by different mechanisms. Superoxide anion-induced apoptosis is FADD-independent and blocked by anti-oxidants and nitric oxide. H2O2 is only cytotoxic when H2O2 detoxification is blocked. ROS-induced apoptosis and necrosis are not independent processes. Manipulation of ROS metabolism determines the mechanism of cell death. Future therapy for liver diseases depends on the mechanism of cell death and must anticipate shifts in the balance between apoptosis and necrosis.

Genetic alterations in Barrett related adenocarcinomas: a search for early tumor markers

L.B. Koppert[1,2], H.W.P.C. van de Meerendonk[2], H. van Dekken[2], H.W. Tilanus[1] and WNM Dinjens[2]. Depts of Surgery[1], Pathology[2], Josephine Nefkens Institute, Erasmus MC, Rotterdam.

Esophageal adenocarcinomas often develop from metaplastic Barrett's esophagus, via low and high grade dysplasia. Only 0.5-1.0% of Barrett patients will eventually develop a carcinoma. Whether these carcinomas develop via mono- or polyclonal expansion is unknown. A search for tumor markers to predict neoplastic progression in Barrett is going on worldwide.
We investigated p16 and p53 tumor suppressor genes in 36 esophagectomy specimens with tumor and adjacent premalignant lesions, either metaplasia (MET), low grade dysplasia (LGD) and/or high grade dysplasia (HGD). DNA was obtained with Laser Capture Microdissection. We performed Loss of Heterozygosity (LOH) analysis of chromosome loci 9p (p16), 17p (p53) and mutation analysis of p53, exons 5 to 8. In 14 of 36 patients, we obtained multiple samples from different areas within the tumor.
Multiple carcinoma samples per patient showed loss of the same p16 allele in 8 out of 11 informative patients, loss of the same p53 allele in 9 out of 9 informative patients and identical p53 mutations in all 9 patients with a mutation. This strongly suggests monocolonal development and therefore the possibility to find tumor markers. In 36 patients p16 loss was found in 80%, 90%, 91% and 91% of MET, LGD, HGD and carcinomas respectively, p53 loss was found in 17%, 59%, 58% and 82% and p53 mutations in 6%, 41%, 52% and 62% respectively. However, premalignant lesions showed slightly different LOH patterns within patients.
In summary, multiple carcinoma samples per patient showed homogeneity concerning p16 and p53 aberrations. In 36 patients, p16 LOH, p53 LOH and p53 mutation percentages were promising for their use as molecular markers. Because of heterogeneity in p16 and p53 aberrations in premalignant lesions within patients, additional gene aberrations, preferably occurring earlier in carcinogenesis than p16 and p53, have to be identified to predict neoplastic progression in Barrett patients.

Optimum treatment strategy for early oesophageal adeno-carcinoma

M. Westerterp[1], C.J. Buskens[1], P. Fockens[2], F.J.W. ten Kate[3], J.J.B. van Lanschot[1]. Dept of Surgery[1], Dept of Gastroenterology[2], Dept of Pathology[3], Academic Medical Center Amsterdam.

Due to increased awareness and advances in diagnostic modalities the detection of early oesophageal cancer is rising.Recently developed endoscopic treatment is inadequate for early lesions suspected for the presence of nodal metastases and surgical resection is considered the treatment of first choice.But the extent of surgical resection is still a matter of debate.To contribute to rational therapeutic decision making we analyzed if a limited transhiatal resection was sufficient to establish locoregional disease control and long-term survival.
Sixty patients with high grade dysplasia (n=11) or T1 adenocarcinoma (n=49),who underwent limited transhiatal resection between 1993 and 2001,were included. Histopathologic characteristics, pattern of lymphatic dissemination, results of surgery, recurrence patternand long term prognosis were analysed.
At pathologic examination, invasion was limimited to the mucosa in 30 patients,while in 30 patients the tumour extended into the submucosa. Of these submucosal tumours, 11 only had minimal submucosal involvement. Mucosal and sm1 cancers never showed lymph node metastases, whereas 12 of the 19 sm2-3 tumours had lymph node involvement.Overall patients with early lesions had a favourable 5-year survival of 73%.The presence of lymph node metastases was an independent prognostic factor for survival
(HR=9.6,p<0.001). Six patients who died due to tumour recurrence all had lymph node metastases at time of resection.Three of these only had locoregional recurrence without distant metastases and therefore might have benefited from a more extensive procedure.
These results suggest that mucosal and sm1 adenocarcinomas are eligible for local endoscopic treatment because of the absence of lymph nodes while for sm2-3 tumours surgical resection is the treatment of choice.The substantial locoregional recurrence without distant dissemination after transhiatal resection is an argument in favour of a more extensive surgical procedure for sm2-3 tumours.

Laparoscopic versus open total mesorectal excision; a case-control study

S.O. Breukink, J.P.E.N. Pierie, C. Hoff, W.J.H.J. Meijerink. Dept of Surgery, Medical Centre Leeuwarden, Leeuwarden.

Because definitive long-term results are not available yet, oncological safety of laparoscopic surgery for treatment of rectal cancer remains unproven. The aim of this prospective non-randomised study was to assess the feasibility and short-term outcome of laparoscopic Total Mesorectal Excision (TME) after preoperative radiotherapy and to compare the results with a historical matched-control group of open TME.
A series of 41 patients with primary rectal cancer underwent laparoscopic TME (LTME) for rectal cancer and were matched with a historical control group of 41 patients who underwent open TME (OTME). Surgical and pathological data were prospectively recorded. Patients in the LTME and OTME groups were matched for age, Dukes classification, and type of resection (low anterior or abdomino-perineal resection).
There was no mortality in the LTME group and 2% mortality in the OTME group. The overall postoperative morbidity was 37% in the LTME group and 51% in the OTME group, including an anastomotic leakage of 5% in the LTME group. The benefits of laparoscopic surgery were shown with a reduction of peroperative blood loss, quicker starting of solid diet and shorter hospitalisation. However, the operative time was increased in the laparoscopic group. A positive circumferential margin was found
in 7% of the LTME group and in 12% of the OTME group.
This study shows that laparoscopic TME is technical feasible and can be performed safely. Next to the general advantages of laparoscopic surgery we show similar surgical radicality by laparoscopic technique compared to open surgery.

Short term results of laparoscopic-assisted versus open restorative (procto-) colectomy: a randomized trial

S. Maartense[1], M.S. Dunker[1], J.F. Slors[1], M.A. Cuesta[2], D.J. Gouma[1] and W.A. Bemelman[1]. Dept of Surgery, Academic Medical Center Amsterdam[1] and Dept of Surgery, Free University Medical Center[2], Amsterdam.

(Procto-) colectomy is the preferred surgical option for the treatment of ulcerative colitis (UC) and familial adenomatous polyposis (FAP). In this randomised trial laparoscopic-assisted restorative (procto-) colectomy is compared with open (procto-) colectomy.
Sixty patients were included in two centers. Primary endpoints were subscales of the SF-36 and the total GIQLI-score 2 and 4 weeks after surgery. Secondary endpoints were operating time, morbidity, morphine requirement and hospital stay.
There were no differences in patient characteristics, except for age. There were no conversions. Median operation time was significantly longer in laparoscopically compared to open surgery (210 respectively 133 minutes; $p<0.001$). Neither morbidity nor postoperative hospital stay differed between the laparoscopic and open group (20% versus 17%, respectively 10 versus 11 days). There was no mortality.
Quality of life returned to baseline levels after 4 weeks in both groups. There was no difference in quality of life on all scales of the SF-36 ($p<0.001$) and total GIQLI-score between groups at 2 and 4 weeks.
Conclusion: Laparoscopic-assisted restorative proctocolectomy can be performed safely. However, there is no difference in morbidity, hospital stay, and postoperative recovery in terms of improvement in QOL.

Sentinel node technique for colorectal carcinoma: colon vs rectum

A.E. Braat[1], dr. J.W.A. Oosterhuis[1], F.C.P. Moll[2], dr. J.E. de Vries[1]. Dept of surgery[1] and pathology[2], Isala clinics location Sophia, Zwolle.

In May 2002 we started using the sentinel node (SN) technique for colorectal carcinoma. Since there are major anatomical differences between the mesocolon and mesorectum, we evaluated the SN technique for colon and rectal carcinoma.
39 consecutive patients, without distant metastasis, were included. We used the so-called 'ex-vivo' technique. After standard resection, 1–2 cc Patent Blue V was injected in the peritumoural, submucosal layer. Within few minutes lymphatics stained blue and the first 1–3 blue lymph nodes were identified as SN. All lymph nodes were examined in a single HE-stained section. If the SN was negative for metastasis, two additional sections were immunostained with keratine CK 7/8.
25 patients with colon carcinoma underwent the procedure. 3 patients were excluded because of peroperatively extensive lymphatic metastasis. In all 22 remaining patients, the SN was identified (100%). In 7 cases the SN contained metastasis, including 2 micrometastasis. This suggests an upstaging of 12% (2/17). In one patient the SN was false negative (accuracy 95%(21/22), sensitivity 88%(7/8)).
14 patients with rectal carcinoma underwent the procedure. In 11 patients, the SN was identified (79%(11/14)). In 1 case the SN contained metastasis, and in 4 cases the SN was false negative (accuracy 80%(7/11), sensitivity 20%(1/5)).
Extensive lymph node metastasis is harder to recognise peroperatively in a rectum specimen compared to a colon specimen. As well, the SN procedure for rectum carcinoma may be negatively affected by the preoperatively given radiotherapy, which possibly obliterates the lymphatic vessels. Furthermore, lymphatic drainage from the rectum may go via collateral pathways to the parailiacal and paracaval lymph nodes.
Conclusions: 1) The SN technique for colon carcinoma is feasible with an identification of 100% and an accuracy of 95%. 2) This results in an upstaging of 12%. 3) The SN technique for rectum carcinoma is in this setting not yet reliable.

Lutetium-177 is the most effective radionuclide for radio-immunotherapy of small peritoneal metastases of colorectal origin

M.J. Koppe[1], A.C. Soede[2], W.J.G. Oyen[2], O.C. Boerman[2], R.P. Bleichrodt[1]. Depts of Surgery[1] and Nuclear Medicine[2], University Medical Center St Radboud, Nijmegen.

Therapeutic efficacy in radioimmunotherapy (RIT) depends, amongst other things, on the radionuclide used. The aim of these studies was to determine the most effective radionuclide for RIT in an experimental model of early-stage peritoneal carcinomatosis of colorectal origin. In nude mice with small intraperitoneal (i.p.) LS174T tumors (1-3 mm), the biodistribution of $^{125/131}$I-, ^{186}Re-, and ^{88}Y-labeled anti-CEA monoclonal antibody MN-14 was determined after intravenous (i.v.) and i.p. administration (five mice/group). The therapeutic efficacy of equitoxic activity doses of ^{131}I-MN-14 (250 µCi), ^{186}Re-MN-14 (250 µCi), ^{177}Lu-MN-14 (225 µCi) and ^{90}Y-MN-14 (85 µCi) after i.p. administration was assessed and compared with that of unlabeled MN-14 (ten mice/group). All radioimmunoconjugates preferentially accumulated in the tumor nodules, both after i.v. and i.p. administration. Uptake of ^{88}Y-MN-14 in liver and spleen was significantly higher than that of ^{186}Re- or ^{131}I-MN-14. Maximal uptake in tumor varied between 58±7% of the injected dose per gram (ID/g) for ^{131}I-MN-14, 83±19% ID/g for ^{186}Re-MN-14 and 148±89% ID/g for ^{88}Y-MN-14. Dosimetric analysis revealed radiation doses guided to the tumor by ^{90}Y-MN-14, ^{186}Re-MN-14, ^{131}I-MN-14 or ^{177}Lu-MN-14 to be 88 Gy, 197 Gy, 312 Gy and 410 Gy respectively. Median survival of mice treated with unlabeled MN-14 was 42 days, whereas median survival of mice treated with ^{186}Re-MN-14, ^{90}Y-MN-14, ^{131}I-MN-14 or ^{177}Lu-MN-14 was 72, 82, 100 and 136 days respectively ($P<0.001$). Four-and-a-half months after tumor induction, no residual disease could be found in eight mice (^{177}Lu, n=4; ^{131}I, n=3; ^{90}Y, n=1) Conclusion: Despite higher uptake of ^{88}Y-MN-14 in tumor, the radiation dose guided to tumor by the ^{90}Y-MN-14 was much lower as compared to that delivered by ^{186}Re-, ^{131}I- or ^{177}Lu-MN-14. Survival of mice treated with ^{90}Y-MN-14 or ^{186}Re-MN-14, however, was similar. ^{177}Lu is the most suitable radionuclide for RIT of small peritoneal metastases.

Prophylactic use of antibiotics in acute (necrotizing) pancreatitis - results of a new meta-analysis-

M.G.H. Besselink, V.B. Nieuwenhuijs, M.Th. de Bruijn, L.P. van Minnen, H.G. Gooszen. Dept of Surgery, University Medical Center Utrecht.

The prophylactic use of antibiotics to prevent infection of pancreatic necrosis in acute pancreatitis has been controversial for many years. In a meta-analysis of 4 randomized clinical trials, Bosscha et al. showed that patients with anticipated severe (necrotizing) pancreatitis should receive prophylactic antibiotics (Ned Tijdschr Geneeskd 2001;145:1982-5). Recently, Isenmann et al. showed in, to date, the largest and the first double blinded and placebo-controlled trial, that there is no beneficial effect of antibiotic prophylaxis (Gastroenterology, in press). The latter study was included in a new meta-analysis. All studies were weighed equally. The absolute risk reduction (ARR), the 95% confidence interval (95%CI) and the number of patients needed to treat (NNT) for the parameters: infected pancreatic necrosis, sepsis and mortality, were calculated.
The prophylactic use of antibiotics led to the following ARR: for infection of pancreatic necrosis: 8% (95%CI: -17–2 , p=ns), for sepsis: 13% (95%CI: -23– -1, p=0,03) and for mortality : 10% (95%CI: -16–3 , p=ns). The NNT to prevent one episode of sepsis was 8.
Conclusion: This updated meta-analysis shows that there is no significant effect of prophylactic use of antibiotics in the prevention of pancreatic necrosis and mortality. The prophylactic use of antibiotics is no longer an obvious step in the treatment of patients with acute pancreatitis.

Dynamic graciloplasty in patients born with an anorectal malformation

S.M.P. Koch , W. van Gemert, Ö Uludag, M.J. Rongen, C.G.M.I. Baeten. Dept of Surgery, Academic Hospital Maastricht.

Objectives of this study are assessment of long-term results of patients born with an ARM and fecal incontinence treated with DGP.
A dynamic graciloplasty (DGP) is a surgical treatment modality offering an opportunity for independence and autonomy in patients born with an anorectal malformation (ARM) that are surgically corrected with unsatisfactory results.
Consecutive patients with fecal incontinence after surgical treatment of ARM and treated later with DGP, were included in this study. Pre-operative assessment was performed. Postoperative follow-up consisted of anorectal manometry and registration of defecation frequency, continence scores and postponement time of defecation.
28 Patients were included with a mean age of 27.7 years with a mean follow-up of 4.6 years. A high ARM was present in 89% of the patients.
All patients were incontinent for stools with a mean frequency of defecation of 6.5 times/day.
The recto-anal inhibition reflex was present in 17% of the patients. The mean sensory threshold during balloon distension was 36 ml and the mean maximum urge threshold was 162 ml.
Satisfactory continence was reached in 35% of the patients, however 7.1% of the patients gained this continence score by additional bowel irrigation. 29% Of the patients were incontinent for loose stool, 36% of the patients were incontinent for formed stool. Satisfactory continence was only achieved in 18% of patients with a high ARM, compared to 100% in patients with a low ARM. Postponement time (0 to 12 min.) and anal squeeze pressures (80 to 128 mmHg) increased significantly after operation. Complications were noted in 57% of the patients. Explantation of the DGP was necessary in 32% of the patients, mainly due to infection of the implant.
Conclusions: Results of DGP for fecal incontinence are reasonable for this specific group of patients with limited treatment options.

The return of bowel function after colonic resection

R.A. de Roo[1], P.A. Neijenhuis[1], H.M. Schuttevaer[2], R.P. Bleichrodt[3]. Dept of Surgery[1] and Radiology[2] Rijnland Ziekenhuis, Leiderdorp, Dept of Surgery[3] University Medical Centre Nijmegen.

After colorectal surgery postoperative feeding in the Netherlands is generally introduced in a graduate way by either strict protocols in which the feeding is increased in set amounts or dictated by clinical signs such as the presence of bowel sounds and passage of flatus and/or stools. In this way normal feeding is not achieved before postoperative day 6.
The aim of this study is to demonstrate the gastrointestinal (GI) tract is recovering faster than suspected by clinical signs alone and that therefore clinical signs should noet be used to assess if postoperative feeding is to be started or increased.
After informed consent a consecutive group of patients after left sided colectomy, with standard anaesthetic protocol including epidural, received a set amount of radio-opaque pellets during 4 days starting on the day of surgery. Radiographs of the abdomen were taken on day 1,3 and 6 postoperatively. The position of the pellets were documented and correlated with the clinical signs for GI function which were documented daily.
35 patients (12 female and 23 male, age range 43-84) were included. On day 1 postop 30% showed radiographic signs of gastrointestinal function whereas on clinical grounds none of the patients had bowel activity. On day 3 60% had resumed GI function clinically whereas radiographically this was 100%. On day 6 in 94% of the patients both modalities showed resumed GI function with most pellets being excreted. 3 patients developed an ileus at some stage during the post-operative period.
Conclusion: Clinical signs are of limited value to decide when to start and increase postoperative feeding in left colonic resections. In the Netherlands normal enteral feeding after colorectal surgery is withheld longer than necessary.

Altana lecture, Dr. P.C. de Groen, M.D

Dr. Piet de Groen is consultant in Gastroenterology and Hepatology as well as in Medical Informatics Research at the Mayo Clinic in Rochester, MN. He is an Associate Professor in Medicine and Gastro-enterology at Mayo Medical School.

Summary of Presentation:
'Nieuwe toepassingen in de Gastroenterologie'

The computer was introduced in healthcare facilities to store and process demographic and financial data. At present, the content of the medical record is being transferred from paper to electronic media, with some facilities being paperless and others still partially paper-based. The physician reads and processes the data as needed during the medical decision-making process. However, the increasing complexity of the medical field and the flood of data expected to be generated by genomic tests will demand that data are preprocessed by computer algorithms before being presented to the physician. Such processing can be based on guidelines – experience of experts converted to computer-based "rules" – or on statistical analysis of the outcome of patients with similar characteristics – "mining" of the data collected in large sets of electronic medical records. At Mayo Clinic Rochester, in collaboration with IBM, we have created a data warehouse that will allow us to store clinical as well as genomic data of millions of patients. In addition, we have created a search engine that can identify subsets of patients with specific features. Expansion of the data within the warehouse and development of new algorithms to analyze and mine across all types of data are the focus of next steps in the collaboration. Eventually, this may lead to computationally-derived, patient-specific recommendations which are available to the physician during the medical decision-making process. Examples relevant for practice and research within Gastroenterology and Hepatology will be discussed.

A closer look at delivered nutrition in the ICU; what you see is not what they get

R.J.M. Strack van Schijndel[1], C. Koster[2], A. Bissumbhar[2], G.C.Melis[1]. Nutrition Support team[1], Student[2], VU University Medical Centre, Amsterdam.

Aims: The objectives of the study were to investigate differences between the amount of enteral nutrition recorded on the flow-sheets and the amount actually delivered to critically ill patients, using a new approach and to discover the causes for discrepancies.
Methods: The study took place in the intensive care unit for adults. The amount of recorded nutrition was compared with the delivered amount on a random day and time. The delivered amount was calculated from the difference in weight of a bag of nutrition between the onset of the bag (full) and the moment of weighing (partly emptied). The recorded given amount was calculated using the time between onset of the bag and the time of weighing the bag (in hours) times the pump setting (ml/hour). A checklist was developed to score reasons for periods of interruption of nutrition.
Results: 100 Bags (nutritional periods) were weighed in 32 patients. Out of a 100 measurements 33 showed an adequate delivery of enteral nutrition. In 56 cases patients received less than 90% and in 11 cases more than 110% of the amount recorded. Discrepancies between recorded and delivered amount of enteral nutrition could not be explained in 72% of the cases. 28% of the discrepancies was caused by diagnostic procedures (21%), gastrointestinal dysfunction, mechanical problems, airway management and nursing procedures.
Conclusions: Results do not agree with similar research, where 100% of the discrepancies, using the same items for observation could be explained for. Discrepancies revealed in this study may be due to inaccuracy of the nutrition pumps or the resistance of the feeding-tubes used. The nutrition pump is calibrated using gastric tubes, while intensive care patients often receive enteral nutrition through a duodenal tube, which is longer and thinner and therefore has a higher resistance. This new pitfall needs further attention.

Evaluation of 6 years use of sodium hydroxide solution to clear partially occluded central venous catheters

P. Balke[1], S.G. Bader[1], T.A.J. Tas[2], C.F. Jonkers-Schuitema[2], H.P. Sauerwein[2]. University of Amsterdam[1], Dept of nutrition and dietetics[2], Nutrition support team, Academic Medical Center, Amsterdam.

Rationale: Occlusion of central venous catheters is not an uncommon problem during long-term home parenteral nutrition. The aim of the study was to investigate the effectiveness of sodium hydroxide (NaOH) for central venous catheter (CVC) occlusion especially in home parenteral nutrition (HPN).
Method: Retrospective study to the use of sodium hydroxide solution to clear partially occluded central venous catheter. Excluded from the study were patients under the age of 18 at the start of HPN and/or patients who use parenteral nutrition less than three months. 45 patients with HPN were included in this study between January 1997 and April 2003. 130 occlusions were registrated in 29 HPN patients.
Results: 95 central venous catheter occlusion were treated with sodium hydroxide. In 73 catheters the occlusion was cleared ($p< 0,001$), whereas 22 out of 130 failed. In 21.575 feeding days 129 occlusions occurred with patients who used fat in their TPN mixture (fig1). The use of fat emulsions in parenteral feeding seems to be the reason for CVC occlusion.
Conclusion: Patients using HPN with fat emulsion are at risk for CVC occlusion. The occlusion can be handled with perfusion of the CVC with 0.1 N NaOH. This technique is safe and will prevent total occlusion and operative removal of the CVC.

Fig 1: the influence of fat in the TPN to the incidence of CVC occlusions

Fat	Feeding days	Occlusions	Incidence of occlusions
Yes	21575	129	1 out of 167
No	7126	1	1 out of 7126

The effect of IGF-I supplemented formula on feeding tolerance and weight gain in preterm infants*

D.A.H. de Gast-Bakker[1], J.B. van Goudoever[1], I. van Vliet[1], S.R.D. van der Schoor[1], M. Alles[2], M. Hooijer[2] and D. Tibboel[1]. Sophia Kinderziekenhuis / ErasmusMC[1], Rotterdam, Numico Research[2], Wageningen.

The gastrointestinal tract of preterm newborns is immature, which results in a sub optimal function with regard to digestion, absorption and feeding tolerance. Early enteral feeding in premature newborns is widely accepted, the infants grow faster, have a less permeable intestine, a better tolerance for enteral feeding and a higher lactase activity. This suggesting that the infant thrives on human milk. Human milk contains several trophic factors among which IGF-I, that stimulate growth and differentiation of the intestine. We hypothesized that IGF-I supplementation of preterm formula would enhance gut function.
We conducted a double blind, randomized, prospective, placebo controlled, single center study in preterm infants with a birth weight of 750-1250 grams, admitted at the NICU within 24 hours after birth. The infants were followed up to a postnatal age of 28 days. Enteral feeding was introduced from postnatal day 2 onwards. Feeding tolerance was quantified by the time needed to reach an intake of 120 ml/kg/day. Growth was measured by quantifying weight gain, head circumference and knemometry and time to regain birth weight.
Informed consent was obtained from 99 infants, of whom 60 were exclusively formula fed and used for final analysis. Patient characteristics were similar in both groups. NEC, length of hospital stay, morbidity and mortality were not statistically different. The following parameters were not significantly different (IGF-I vs placebo): days to full enteral feeding (11,5 vs 12), days to regain birth weight (8 vs 8) and growth parameters over 28 days: weight gain in g/kg/day (7,5 vs 6,4), head circumference in mm/kg/day (0,096 vs 0,098) and knemometry in mm/kg/day (0,25 vs 0,24).
Early introduction of enteral feeding in premature newborns results in a rapid return of weight after initial weight loss. IGF-I supplementation of preterm formula does not improve feeding tolerance or growth rates in premature infants in their first weeks of life.

Plasma glutamine response to enteral and parenteral administration of L-alanyl-L-glutamine in pre-operative patients

P.G. Boelens[1], G.C. Melis[1], J.R.M. van der Sijp[1], N.E.P. Deutz[2], P.A.M. van Leeuwen[1]. Dept of Surgery, VUMC[1], Amsterdam and Dept of Surgery, UM [2] , Maastricht.

Glutamine (Gln) is an important amino acid especially during stress such as surgery. Many studies show clinical benefits, e.g. a reduced infections and mortality, of extra Gln. However, most artificial feedings only contain low Gln concentrations because of its aqueous instability. The dipeptide L-alanyl-L-glutamine (Ala-Gln), which is stable in watery solutions, may be a good alternative. Since no enteral kinetic data are available yet, we compared a parenteral and enteral infusion of the dipeptide on the plasma glutamine response.
Five pre-operative patients received a self-migrating jejunal tube (Bengmark, Nutricia, Zoetermeer) for the enteral infusion. A venous line was given for the parenteral infusion and an arterial line for blood sampling. During a 4-hour infusion of 20g/100ml Ala-Gln (Dipeptiven, Fresenius Kabi, Germany) in 400ml NaCl 0.9%, blood samples were taken for amino acid determination by HPLC. ANOVA for repeated measures was performed with a paired T-test if significant. $P<0.05$ was significant. (mean ± SD)
Baseline plasma Gln was 597±160 µmol/l before the parenteral infusion and 544±71 µmol/l before the enteral infusion (n.s.). Both infusions had a significant increment in plasma Gln response in time. During the parenteral infusion, plasma Gln was higher than t=0 at 30 minutes (min) after the start of infusion and still higher at t=270 with a peak of 480±173 µmol/l at t=240. During the enteral infusion, plasma Gln was significantly higher than t=0 from 45 min after the start of infusion until t=250, with a peak rise of 250±74 µmol/l at 90 min. A comparison of enteral and parenteral infusions at the corresponding points in time showed that plasma Gln was significantly different from t=90 until t=270. In conclusion, both infusions of Ala-Gln resulted in increased plasma glutamine as compared to baseline. Plasma glutamine was lower when given enterally, possibly due to a different utilisation of the dipeptide by the gut.

Plasma arginine concentrations and de novo arginine production from citrulline are lowered during sepsis

Y.C. Luiking[1], M. Poeze[1], L. Steens[2], G. Ramsay[1], N.E.P. Deutz[1]. Depts of Surgery[1] and Intensive Care[2], University Hospital Maastricht and University Maastricht.

L-Arginine (L-Arg) is an important precursor of nitric oxide (NO) and protein synthesis. L-Arg is produced in the body (mainly kidney) by *de novo* production from Citrulline (Cit) and by protein breakdown. Cit is mainly produced from gut Glutamine conversion. This study was aimed at comparing Arg metabolism in septic patients versus non-septic controls in the ICU.
13 ICU patients were studied: 8 with severe sepsis/septic shock (sepsis) and 5 non-septic controls (2 recovered from pulmonary failure, 2 exacerbations COPD, 1 neurotrauma; non-sepsis). Metabolism was measured within 48h of diagnosis, using stable isotope techniques. Arg and Cit production and conversion rates were examined using primed-continuous (2h) infusion of L-[*guanidino*-$^{15}N_2$-$^{2}H_2$]Arg and L-[*ureido*-^{13}C]Cit and subsequent measurements of arterial amino acid concentrations and tracer-tracee ratios using LC-MS. NO production is measured as Arg to Cit conversion; *de novo* Arg production as Cit to Arg conversion. 2-way Anova.
Plasma Arg levels were lower during sepsis (47.7±4.4 vs 68.2±5.1 μM in non-sepsis; $P<0.01$), but whole body Arg and NO production were not different between groups. In contrast, whole body Cit and *de novo* Arg production were both lower during sepsis (Cit: 6.2±1.0 and 11.4±1.2 μmol/kg/h, in sepsis and non-sepsis, resp. ($P<0.01$); *de novo* Arg: 5.8±2.9 and 17.0±3.0 μmol/kg/h in sepsis and non-sepsis, resp. ($P<0.05$)). Compared with healthy subjects (Tau, J Clin Invest, 2000), *de novo* Arg production is increased about 3-fold in our non-sepsis controls and NO production is 2-fold higher in both ICU-patient groups.
Conclusions: Lowered plasma Arg levels in septic patients do not coincide with increased *de novo* Arg production, higher NO production or altered total Arg production. This unresponsiveness to increase endogenous Arg production in sepsis results in an Arg deficiency state. The reduced Cit production during sepsis could be related to compromised gut glutamine metabolism.

Arginine metabolism in human wounds: acute versus chronic wounds

I.B.J.G. Debats[1], N.E.P. Deutz[2], W.D. Boeckx[1], R.R.W.J. vd Hulst[1]. Dept of Plastic Surgery[1] and Surgery[2], Academic Hospital Maastricht.

Experimental studies show that the amino acid Arginine plays an important role in wound healing. To better understand the patho-physiology of chronic wound healing in humans we studied arginine metabolism in patients with chronic wounds and compared this with the metabolism of acute wound healing in humans.
Thirty patients with chronic wounds, mean age 58±11, enrolled our study. We collected a blood sample and wound fluid sample under standardized conditions in 13 men and 17 women. In the samples the concentrations of arginine (Arg), citrulline (Cit) and ornithine (Orn) were analyzed with HPLC. Eight healthy subjects, 6 men and 2 women, mean age 50±18 with an acute wound, were used as control group.
In the control group the plasma amino acid levels were (mean ± SEM): 84±13.2 µmol/l (Arg), 28±3.4 µmol/l (Cit) and 69±8.3 µmol/l (Orn), the wound fluid concentrations (µmol/l) were (mean ± SEM): 73±17.0 (Arg), 66±14.3 (Cit) and 131±17.4 (Orn).
The plasma concentrations (µmol/l) in patients with chronic wounds were (mean ± SEM): 72±5.2 (Arg), 41±16.3 (Cit),111±42.5 (Orn) and in wound fluid: 82±13.9 (Arg), 214±51.6 (Cit) and 358±75.2 (Orn).
The woundfluid concentrations of Cit and Orn were significantly higher in chronic wounds compared to acute wounds (Mann-Whitney $p<0.05$). There were no differences in plasma amino acid concentrations between the two groups.
Orn and Cit, end products of both metabolic pathways of Arg, are enhanced in wound fluid of chronic wounds compared to acute wounds. A simultaneous and enhanced stimulation of these two pathways could suggest an explanation for delayed wound healing in chronic wounds.

Ornithine pathway is stimulated in human wound healing during Arginine suppletion

I.B.J.G. Debats[1], N.E.P. Deutz[2], W.D. Boeckx[1], R.R.W.J. v.d. Hulst[1].
Dept of Plastic Surgery[1] and Surgery[2], Academic hospital Maastricht.

Arginine (Arg) is an important semi-essential amino acid in acute wound healing. It has been extensively studied in animal studies. The aim of this study was to investigate the effect of oral Arg-suppletion on Arg-metabolism in human wound healing.
Thirteen healthy patients, 8 men and 5 women, mean age: 49±19, were randomized in a double blind, placebo controlled study. All patients underwent a skin transplantation. During five days they were given a solution enriched with 30 grams of Arg or an isonitrogenous amount of Alanine. Bloodsamples were taken pre-operatively and at day 2 and 5 after surgery. A woundfluid sample was collected on day 2 after surgery. In all samples concentrations of Arg and its metabolites, Citrulline (Cit) and Ornithine (Orn) were analyzed.
There was no difference in mean pre-operative plasma Arg, Cit and Orn between both groups. Plasma Arg and Orn on day two were higher in Arg-suppletion group (Mann-Whitney $p<0.05$).
Woundfluid Orn was higher in Arg-suppletion group (Mann-Whitney $p<0.05$). In the Arg-suppletion group wound Cit/Orn-ratio was about two times lower compared to placebo (0.29±0.06 vs. 0.55±0.12).
In this model for acute wound healing in humans both end products of Arg-metabolism, Cit and Orn, are higher in wound fluid compared to plasma. This suggests that both metabolic pathways are active and that Nitric Oxide and hydroxyproline are produced in the wound. In addition these results demonstrate increased arginase activity in wounds during Arg-suppletion.

Decreased phenylalanine clearance rate and generalized hyperaminoacidemia following hepatectomy for malignancies in man

M.C.G. van de Poll[1], Y.C. Luiking[1], S.J. Wigmore[2], D.N. Redhead[3], O.J. Garden[2], 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, Maastricht Universty[1],The netherlands, Surgery[2], radiology[3], Royal Infirmary, Edinburgh, Scotland.

Following hepatectomy the liver regenerates within 3 months. However, meanwhile metabolic demands must be met by a substantially smaller liver volume. We previously showed that metabolic liver function, represented by urea synthesis and phenylalanine (PHE) hydroxylation, is remarkably well preserved directly following hepatectomy in man. In addition whole body protein synthesis and breakdown were unchanged following hepatectomy. However, the mechanisms behind this adaptive response remain unclear.
14 Patients scheduled for hepatectomy because of hepatic malignancies were studied. Six patients underwent major hepatectomy, 8 underwent simple metastasectomy or were regarded irresectable during laparotomy. These patients served as controls. During surgery a primed continuous infusion of 2H5-PHE was administered for 6 hours in 8 patients (3 resected). Blood was sampled hourly from an indwelling radial artery catheter. Amino acid concentrations were measured by HP-LC, isotopic enrichment by LC-MS. PHE clearance rate, i.e. the amount of plasma cleared of PHE per minute, was defined as the quotient of PHE rate of disappearance and arterial PHE plasma concentration.
PHE clearance (ml/kg/min±SEM) before hepatectomy was 0.93±0.21, in patients who eventually were resected (n=3) and 1.01±0.07 in controls (n=5) (NS, Mann-Whitney U test). After hepatectomy PHE clearance remained unchanged in the control group (1.04±0.21) while a significant decrease was observed in the patients who underwent hepatectomy (0.48±0.21, $p<0.05$). This was accompanied by a significant increase compared to controls in plasma concentration of PHE (68.2±5.4, n=6, vs 40.7±3.8 µmol/l, n=8, $p<0.01$) and of several other amino acids.
Conclusions: Phenylalanine clearance is significantly decreased following hepatectomy in man. This probably is effectuated to deliver more substrate to the liver remnant and keep whole body protein turnover in steady state.

Asymmetrical dimethylarginine reflects hepatic function in patients undergoing liver transplantation

M.P.C. Siroen[1], M.C. Warlé[2], T. Teerlink[3], R.J. Nijveldt[1], H.W. Tilanus[2], H.J. Metselaar[4], J.R.M. van der Sijp[1], S. Meijer[1], B. van der Hoven[5], P.A.M. van Leeuwen[1]. Depts of Surgery[1] and Clinical Chemistry[3], VU University Medical Center, Amsterdam, and Depts of Surgery[2], Gastroenterology and Hepatology[4], and Surgical Intensive Care Unit[5], Erasmus Medical Center, Rotterdam.

Asymmetrical dimethylarginine (ADMA) has been recognized as an endogenous inhibitor of the arginine-nitric oxide (NO) pathway. Its concentration is tightly regulated by urinary excretion and degradation by the enzyme dimethylarginine dimethylaminohydrolase, which is highly expressed in the liver. Considering the liver as a crucial organ in the clearing of ADMA, we hypothesized increased ADMA levels during hepatic failure and a decline of ADMA concentrations after liver transplantation. Furthermore, since the arginine-NO pathway plays a critical role in function of the transplanted liver graft, high ADMA concentrations might reduce availability of NO, possibly leading to liver allograft rejection. To test these hypotheses, we investigated the course of ADMA concentrations in 42 patients undergoing liver transplantation.
ADMA concentrations (geometric mean; 95% CI) were higher in all patients on the day before transplantation (0.77 μM; 0.33-1.76) compared to healthy volunteers (0.41 μM; 0.32-0.55, $p<0.001$) and decreased on the first postoperative day (0.55 μM; 0.31-1.00, $p<0.001$). In patients with acute (n=7) hepatic failure, preoperative ADMA levels were higher compared to patients who underwent liver transplantation due to chronic (n=35) hepatic failure (1.26 μM; 0.54-2.89 vs 0.69 μM; 0.35-1.39, p=0.003). In patients with episodes of rejection (n=13), ADMA concentrations increased from day 7 (0.71 μM; 0.48-1.04) to day 14 (0.86 μM; 0.78-1.28, p=0.032). Furthermore, ADMA levels were higher in the rejectors on day 14 (p=0.012), day 21 (p=0.071), and day 28 (p=0.027) compared to non-rejectors (n=29).
In conclusion, patients suffering from hepatic failure have elevated ADMA levels which decrease after liver transplantation, indicating an important role for the liver in the clearing of ADMA. Moreover, increasing ADMA concentrations in the posttransplantation period reflect dysfunction of the transplanted liver graft and may predict allograft rejection.

Alterations in gene expression profile of the gut due to the starvation

M. Sokolovic[1], T.B.M. Hakvoort[1], L.A. Gilhuijs-Pederson[2], D. Wehkamp[2], A.H.C. van Kampen[2], W.H. Lamers[1]. AMC Liver Center[1] and Bioinformatics Laboratory[2] , Academic Medical Center, Amsterdam.

The objective of this study is to begin to understand the complexity of the adaptive response of the gut to food deprivation. As a first step, we therefore estimated the mRNA abundance in the small intestines under fed and fasting conditions. Mice were fed *ad libitum* or fasted 24 and 72 hours. Total RNA was isolated from the intestines of these animals using CsCl-gradient centrifugation. mRNA abundance was estimated using DNA-microarray technology, with 22000 genes on the chip (Agilent).
Following an ANOVA-based normalisation procedures, the genes that were differentially expressed, that is, up- or down-regulated due to fasting, were identified. The data were validated for a subset of the genes by immunohistochemistry and Real-Time PCR. Among the differentially expressed genes were mRNAs of genes involved in the innate immune response (MHC class 2 beta (5.8x↓)), apoptosis (Caspase 6 (5x↓)), transcription factors (RXRa (8.3x↑); Tcf 4 (5x↑); Tcf21 (2x↓); NfkbI (4.5x↑)), signalling (Cyclin G2 (3.7x↓); huntingtin (8.5x↑)) and intermediate metabolism (Pdk (7x↑); PepCK (6x↑); GS (6x↑) Aldh1a1 (3.7x↓)), suggesting that all these pathways may be involved in the response to food deprivation.
In a first attempt to cluster the data in order to find biological patterns we found genes (Mcl-1, Bcl-2a, Bad, Bcl-xL, Bok, Bid) that function as apoptotic agonists in the apoptosis pathway all were more than two times up-regulated. Components within the caspase-cascade (Casp1, Casp6) were down-regulated more than four times. These observations could help explaining the way the intestinal cells modify their apoptotic pathway during the starvation.

An explorative study on the effect of enzyme supplementation in patients recovered from acute pancreatitis

T. Symersky, C.B.H.W. Lamers, A.A.M. Masclee. Dept of Gastro-enterology-Hepatology, Leiden University Medical Center.

After recovery from acute edematous pancreatitis (AP), a subset of patients retain partial loss of exocrine pancreatic function. Various abdominal symptoms may be related to this functional impairment, and when recognized may be alleviated by pancreas enzyme supplementation.
To compare, in an explorative, placebo controlled study, the influence of pancreatin (lipase 25000, Solvay Pharma) on quality of life (QoL) and abdominal symptoms in patients recovered from acute pancreatitis, with a subsequent exocrine pancreatic dysfunction.
Eighteen patients (9 F, mean age 57±13 yr) recovered from AP (4.4 ±0.6 yr after attack) with exocrine pancreatic dysfunction (fecal fat > 7 g/24 hr and/or urinary PABA recovery < 50%) were recruited. The etiology of the AP was biliary (39%), post-ERCP (17%), alcoholic (16%) or idiopathic (28%). Subjects were randomized to either pancreatin or placebo (plac) tid for 12 weeks. At each 4-week visit the Gastrointestinal QoL Index (GIQLI) was scored. Abdominal symptoms (scale 0-10) and dietary intake records were kept prior to each visit, for 7 and 3 days resp At 12 weeks function tests were repeated.
After 4 weeks the GIQLI score (max 144) rose from 91±7 to 104±5 in the pancreatin group, and from 113±6 to 117±6 in the plac group (non-significant -NS). At 4 weeks abdominal pain score decreased sign. ($p<0.05$) in the pancreatin group (from 2.7±0.7 to 1.3±0.3) but not with plac (from 1.2±0.6 to 1.4±0.5). This was also true for other abdominal symptoms but differences were NS. The coefficient of fat absorption increased from 71±6 to 76±6% (NS) in the pancreatin group, but not in the plac group (84±5% to 85±6%).
This study shows that pancreatin significantly reduces abdominal symptoms and increases QoL (NS) in a group of patients recovered from AP with previously unrecognized mild to moderately impaired exocrine function. Further confirmation of the effect of enzyme supplementation in a larger group of patients after AP is warranted.

Lipid-dependent regulation of transporter gene expression in the small intestine

H. van den Bosch, M. Bünger, G. Hooiveld, M. Müller. Nutrition, Metabolism & Genomics group, Wageningen University.

The bioavailability of nutrients and potentially toxic food components is determined by transporter proteins located in the cell membranes of enterocytes. It has become evident that certain nutrients such as fatty acids not only serve as building blocks or energy resources, but also regulate gene expression. Fatty acids activate the nuclear receptor PPARa, which in turn may influence gene transcription. In the present study we investigated the effects of fatty acids on gene expression in the small intestine.
Prolonged fasting is characterized by increased concentrations of fatty acids in plasma. Mice were therefore fasted for various periods up to 24 hours. Intestinal RNA was isolated and hybridized on Agilent 22K oligo arrays. Genes that were differentially expressed were picked out of the dataset. 24 Hours of fasting resulted in 5-fold increased serum free fatty acid levels. Micro-array data combined with quantitative Real-Time PCR revealed that the expression levels of about 20 transporter genes were changed after 24 hours of fasting. The gene encoding for the intestinal fatty acid transporter Fatp4 was 2-fold down regulated. The expressing of Ppara was 2.5-fold increased. In addition, mRNA levels of genes for glucose, nucleotides, sodium phosphate, iron, amino acids and vitamin transporters were more than 1.8-fold changed upon fasting. For in vitro experiments primary mouse intestinal epithelial cells (IEC's) and human Caco2 cells were used. Cells were treated for 24 hours with the synthetic PPARa ligand WY-14,643. This resulted in an up regulation of the FATP4 and the PPARa gene expression in both cell lines.
Fasting influences the expression levels of a number of transporter proteins, indicating that the bioavailability of nutrients may be altered. Furthermore, the synthetic PPARa ligand Wy-14,643 upregulates the gene expression of PPARa and FATP4 in vitro.

No indications for imbalance in membrane essential fatty acids (EFA) or altered EFA metabolism in two murine models for cystic fibrosis*

A. Werner[1], M.E.J. Bongers[1], M.J.C. Bijvelds[2], M. Sinaasappel[3], F. Stellaard[1], H.R. de Jonge[2], H.J. Verkade[1]. Dept Pediatric Gastro-enterology[1], Academic Hospital, Groningen, Dept Biochemistry[2] and Dept Pediatrics[3] , Erasmus University Medical Center, Rotterdam.

A membrane EFA imbalance was reported in CF-affected tissues of $cftr^{-/-UNC}$ mice compared to non-littermate controls (PNAS '99;13995). Oral docosahexaenoic acid (DHA) corrected this imbalance and allegedly improved CF symptoms. However, it remains unclear if a membrane EFA imbalance is inherent to the CF phenotype, and if EFA metabolism is impaired in CF.
We analyzed membrane EFA composition in two alternative CF mouse models: $cftr^{-/-CAM}$ and ΔF508 mice and their littermate controls. EFA metabolism was quantified in $cftr^{-/-}$ and $cftr^{+/+}$ littermates.
Lipid profiles were analyzed in pancreas, lung and gut of chow-fed C57Bl/6;129 $cftr^{-/-CAM}$ mice, FVB;129 homozygous ΔF508 mice and sex-matched littermates, and in liquid diet-weaned $cftr^{-/-}$ and $cftr^{+/+}$ littermates and wild-type C57Bl/6 mice. To quantify EFA metabolism *in vivo*, ^{13}C-linoleic (LA) and ^{13}C-α-linolenic acid (ALA) was given orally to $cftr^{-/-}$ and $cftr^{+/+}$ littermates. After 24h, ^{13}C-enrichment of LA, ALA and their metabolites arachidonic acid (AA) and DHA was assessed by mass spectrometry.
We found no significant differences in membrane LA, ALA, AA or DHA levels in pancreas, lung and gut of chow-fed CF mouse-models compared to their respective controls. AA and DHA contents in membranes of liquid diet-weaned $cftr^{-/-}$ and $cftr^{+/+}$ littermates were similar, but consistently higher than in age- and diet-matched C57Bl/6 wild-type mice ($P<0.01$ for all tissues). 24h after label ingestion, ^{13}C-enrichment of LA and ALA was equal in CF-affected tissues of $cftr^{-/-}$ and $cftr^{+/+}$ mice. ^{13}C-enrichment of AA and DHA was also similar, indicating comparable rates of LA and ALA metabolism in $cftr^{-/-}$ and $cftr^{+/+}$ mice.
We conclude that membrane EFA composition in mice is strongly determined by genetic background, underlining the importance of littermate controls. A membrane EFA imbalance in CF-affected tissues is not inherent to CF. *In vivo* stable isotope experiments indicate that $cftr^{-/-}$ mice adequately absorb and metabolize EFA.

The nutritional gab between ICU and general hospital ward

G.C. Melis[1], K.A.C. Berk[2], J.C.M. van der Steen[2], R.J.M. Strack van Schijndel[1]. Nutrition Support Team[1], Student[2], VU university Medical Centre, Amsterdam.

Aims: Nutrition protocols have been implemented in most intensive care units (ICU's). However, little is known about the continuation of nutritional care after transferral from the ICU to the general hospital ward. The objective of this study was to investigate nutritional care after transfer.
Methods: Interviews were held with disciplines involved in the care for patients before and after transfer from the ICU. Using the information obtained from these interviews, a checklist was compiled which was then used to observe the patient transfer process during a 7-day period: 1 day before and 6 days after transfer. The difference between energy-intake and energy needs was used as an indicator of quality of the transfer process. Indirect calorimetry was performed once, before transfer, to determine energy-needs.
Results: From the interviews it was concluded that the policy of nutritional care after transfer was unclear and that a protocol was lacking. 9 ICU patients were observed. In all cases the patients received enteral tube feeding during their stay at the ICU. In 3 of 9 cases enteral feeding was discontinued on the general ward. These patients showed a decrease in energy intake resulting in an energy-deficit of more than 80%. No dieticians were involved in the transfer process. For 2 of 9 patients a dietician was consulted afterwards on the hospital ward.
Conclusions: This study showed an inadequate quality of continuing nutritional care after transfer from the ICU to general hospital ward. Often there was a discontinuation of enteral feeding and consequently an inadequate energy intake in transferred patients. A recommendation to involve dieticians in the planning and supervising of the transfer process has been made as a result of this study.

Excessive belching in aerophagia visualized by oesophageal impedance monitoring: the concept of oesophageal belching

B.L.A.M. Weusten[1], J. Silny[2], L.M.A. Akkermans[3], A.J.P.M. Smout[3]. Dept of Internal Medicine[1], St. Antonius Hospital, Nieuwegein, The Netherlands, Aachen University of Technology[2], FEMU, Aachen, Germany and Gastrointestinal Motility Unit[3], University Medical Center, Utrecht, The Netherlands.

The mechanisms of excessive belching is hitherto poorly understood. In an attempt to clarify the pathophysiology of excessive belching, we used intra-oesophageal electrical impedance monitoring (a technology making it possible to monitor the passage of air through the oesophagus) in 2 male patients with aerophagia (age 43 and 61) and 11 healthy controls (4 m, 7 f, age 18 – 43). A 6-channel ambulatory impedance system was used. The recording segments were located at 0-2, 2-4, 4-6, 10-12, 14-16, 17-19 above the LOS. Each recording channel was sampled at 1000 Hz. In all a protocol was carried out consisting of a fasting recording period of 45 minutes followed by a standardized meal and a 90 minutes postprandial period.
Three distinct patterns of passage of air could be discerned. Pattern A, consisting of a sudden increase in impedance followed by a decrease moving in aboral direction reflected the passage of a certain amount of air swallowed together with a bolus. In pattern B, more sporadical waves of sudden high increments of impedance travelled from the distal to the proximal oesophagus, representing venting of gas from the stomach (normal belching). Patterns A and B were encountered as often in controls as in the patients. In pattern C, only encountered in patients (53x and 38x, resp.) and coinciding with observed belching, sudden, high increments of oesophageal impedance were recorded on all impedance channels, beginning at the most proximal recording segment, and very rapidly moving distally along the oesophagus, implicating the passage of air in aboral direction. The aboral movement of air was immediately followed by clearance of the air bolus in opposite direction. This pattern of rapid influx and efflux of air in the oesophagus can be referred to as oesophageal belching and was the mechanism of excessive belching in the patients with aerophagia.
Conclusion: belching in aerophagia is the result of a mechanism distinctly different from regular belching

Efficacy of Activated Recombinant Factor VII (rFVIIa; Novoseven®) in Cirrhotic Patients with Upper Gastrointestinal Bleeding: A Randomized Placebo-controlled Double-blind Multicenter Trial

D. Thabut, R. de Franchis, F. Bendtsen, G. d'Amico, A. Albillos, J.G. Abraldes, S. Fabricius, P.C.J. ter Borg[1], H.R. van Buuren[1], J. Bosch, on behalf of a European Study Group. Erasmus Medical Centre[1], Rotterdam.

Preliminary results show that rFVIIa may reduce bleeding in cirrhotic patients. This trial aimed to determine the efficacy and safety of rFVIIa in cirrhotic patients with variceal and non-variceal upper gastrointestinal bleeding (UGIB). 245 cirrhotic patients (Child-Pugh A=20%), B=52%, C=28%) with upper gastrointestinal bleeding (UGIB)(variceal 66%, non-variceal 34%) were equally randomized to receive 8 doses of 100 µg/kg rFVIIa or placebo in addition to pharmacologic and endoscopic treatment. Primary composite endpoint: failure to control UGIB within 24h post-dosing, or failure to prevent rebleeding between 24h and day-5, or death within 5 days. Baseline characteristics were similar between groups. In the sub-group of Child-Pugh B and C variceal bleeders, significantly fewer patients in the rFVIIa-treated group failed on the composite end-point (p=0.03) and the 24h-bleeding control endpoint (p=0.01) relative to placebo. rFVIIa did not improve the efficacy of standard treatment in Child-Pugh grade A cirrhotic patients, and no significant effect was found when analysing all applicable patients. Incidences of adverse events including thrombo-embolic event were similar, and there were no significant differences in 5-day or 42-day mortality. In conclusion, exploratory analyses in Child-Pugh B and C cirrhotic patients indicated that administration of rFVIIa was safe and significantly reduced the proportion of patients who failed to control variceal bleeding. Further studies are needed to verify these findings.

Esomeprazole continuous versus on demand maintenance therapy in 1052 gastro-oesophageal reflux disease patients: similar satisfaction but superior quality of life for once daily treatmen

L.G.J.B. Engels[1], E.C. Klinkenberg-Knol[2], C.P.M. Dekkers[3], J.A. Beker[3], T.G. Tan[3], R.J. Timmerman[3], P.W.E. Haeck[3]. Dept of Gastro-enterology[1], Maasland Hospital, SittardVU Medical Centre[2], Amsterdam, On behalf of the Brilliant study group[3].

Gastro-Oesophageal Reflux Disease (GORD) is a common health care problem, with a majority of patients experiencing relapse within 6 months regardless of endoscopic status.
The aim of the study was to compare continuous esomeprazole 20mg once daily to esomeprazole 40mg on demand as 6 month maintenance regimens in Endoscopic Negative Reflux Disease patients (ENRD) and in patients with Reflux Oesophagitis (RO) LA grade A or B, with regard to patient satisfaction, symptoms and QoL. In this multicentre, invest-tigator-blind study, 596 ENRD and 574 RO patients were treated in a run-in period with esomeprazole 40mg once daily during 2,4 or 8 weeks, until reaching sustained symptom relief (maximum 1 day mild heartburn symptoms in the last 7 days) and sufficient satisfaction. After the run-in treatment, patients were randomised to receive esomeprazole 40mg on demand or 20mg continuous therapy for 6 months. During the study, patient satisfaction with treatment, GORD symptoms and QoL (QOLRAD questionnaire) were evaluated.
After the esomeprazole 40mg run-in period, the cumulative proportion of 1170 enrolled patients experiencing sustained symptom relief was 71%, 84% and 89% after week 2, 4 and 8 respectively, with no difference between ENRD and RO patients. 1052 patients were randomised to maintenance treatment. After 6 months, 89% of the patients indicated they were overall quite satisfied or completely satisfied with treatment, with no statistical difference between treatment regimens. As expected, after a run-in period the randomised patients showed improvement on all dimensions of QoL. In both ENRD and RO patients the continuous treatment regimen was significantly better than the on demand regimen in maintaining the improved QoL.
Concluding, in this study, after 6 months maintenance treatment, continuous esomeprazole 20mg was superior to on demand esome-prazole 40mg in maintaining QoL in ENRD and RO patients, while both regimens provided similar patient satisfaction

Prospective comparison of hydrogen peroxide-enhanced 3D endo-anal ultrasonography, endoanal MR imaging and surgical exploration for perianal fistulas

R.L. West[1], D.D.E. Zimmerman[2], S. Dwarkasing[3], S.M. Hussain[3], W.C.J. Hop[4], W.R Schouten[2], E.J. Kuipers[1], R.J.F. Felt-Bersma[1]. Depts of Gastroenterology and Hepatology[1], Surgery[2], Radiology[3], Epidemiology and Biostatistics[4], Erasmus MC/University Medical Center Rotterdam.

In a previous study hydrogen peroxide-enhanced 3D endoanal ultrasonography (3D HPUS) and endoanal MRI showed comparable results in preoperative assessment of perianal fistulas. The aim of this study was to compare these results to the surgical findings.
Twenty-one patients (aged 26-71) with symptoms of a cryptoglandular perianal fistula and an external opening underwent 3D HPUS, endoanal MRI and surgical exploration. The results were assessed separately by observers blinded for each other's findings. Each fistula was described with notice of the following characteristics: classification of the primary fistula tract according to Parks (intersphincteric, transsphincteric, extra-sphincteric, suprasphincteric) or not classified, presence of secondary tracts (circular or linear) and location of an internal opening.
The median time between 3D HPUS and endoanal MRI was 66 days (IQR 21-160), the median time between the last study and surgery was 154 days (IQR 95-189). Agreement for the classification of the primary fistula tract was 81% for 3D HPUS and surgery, 90% for endoanal MRI and surgery as well as for 3D HPUS and endoanal MRI. For secondary tracts agreement was 67% for 3D HPUS and surgery, 57% for endoanal MRI and surgery and 71% for 3D HPUS and endoanal MRI in case of circular tracts, and 76% for 3D HPUS and surgery, 81% for endoanal MRI and surgery and 71% for 3D HPUS and endoanal MRI in case of linear tracts. Agreement for the location of an internal opening was 86% for 3D HPUS and surgery as well as for endoanal MRI and surgery and 90% for 3D HPUS and endoanal MRI.
Conclusions: For evaluating perianal fistulas 3D HPUS and endoanal MRI have a good agreement especially for the classification of the primary fistula tract and the location of an internal opening. These results also show good agreement when compared to surgical findings. Therefore 3D HPUS and endoanal MRI can both be used as a reliable method for preoperative evaluation of perianal fistulas.

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

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.

Our previous study showed that 3D transanal ultrasonography (TU) can assess anal sphincter volumes and that these are greater in men than in women but parity had no effect. The aim of this study was to determine the volume of the anal sphincters and anal pressure profile in incontinent parous females and to compare these results to continent parous females.
Thirty parous females (mean age 50.7, range 27-78 years) were recruited, 16 incontinent and 14 continent. Bowel habits were assessed by means of a questionnaire. 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. Anterior and posterior sphincter length were determined on TU as was the external sphincter thickness (EST). Resting and maximal squeeze pressure and length of the anal sphincter were assessed by manometry. Results were compared using the Kruskall Wallis Test (median, p-value).
Incontinent females all had a Vaizey score ≥ 16 and an anterior sphincter defect. Incontinent females had a smaller EAS volume but this was not significant (3.5 cm3 vs. 4.2 cm3, p=0.25). There was no significant difference in PR or IAS volume. Anterior sphincter length was significantly shorter in incontinent females (0.4 cm vs. 0.7 cm, p=0.001). No differences were found for posterior sphincter length. Mean EST was significantly smaller in incontinent females (0.5 cm vs. 0.6 cm, p=0.03). Resting and maximum squeeze pressure were significantly lower in incontinent females (39 mmHg vs. 89 mmHg, p<0.001 and 84 mmHg vs.144 mmHg, p=0.003). No significant difference was found for sphincter length measured by manometry.
Conclusions: There were no significant differences in anal sphincter volumes. However incontinent females did have a smaller anterior sphincter length and mean EST due to an anterior sphincter defect. Manometry results showed a lower resting and maximum squeeze pressure.

Constipation after hysterectomy

F.G.M. Timmermans[1], P.P.J. van der Veek[1], P.T.M. Weijenborg[2] and A.A.M. Masclee[1]. Depts of Gastroenterology and Hepatology[1] and Gynecology[2], Leiden Universty Medical Center.

It has been suggested that constipation is common in patients who underwent a hysterectomy. However, the prevalence of these symptoms and their impact on Quality of Life (QOL) compared to the general population is unclear. Our aim was to determine the incidence of constipation, demographic variables and Quality of Life (QOL) in patients who underwent a hysterectomy at the Leiden University Medical Center between January 1997 and December 2001. Detailed questionnaires were sent to 281 eligible patients (malignancy was excluded) to assess demographics, pre- and post-operative bowel habits, the presence of Irritable Bowel Syndrome (IBS, according to Rome II) and QOL (RAND-36). Constipation was defined as <3 bowel movements per week and/or as evacuation disorder (e.g. straining, incomplete or digital evacuation etc.). One hundred and ninety-two patients (age 50.7 ± 0.7 yr) returned their questionnaires (response rate 68%). Fifty-nine patients (31%) had vaginal and 133 patients (69%) abdominal hysterectomy. Thirty-nine patients (20%) had constipation before hysterectomy, compared to 59 (31%) after the operation ($p=0.02$). In 13 out of 39 patients (33%) previously having constipation, bowel habits normalized after the operation. However, 33 of 153 (22%) asymptomatic patients newly developed constipation. Neither age nor Body Mass Index, parity or type of operation correlated with the occurrence of post-operative constipation. Overall, 9% of post-hysterectomy patients had IBS, compared to 8% in the general population (NS), suggesting that hysterectomy is not a risk factor for IBS. Patients with newly developed constipation had significantly impaired QOL compared to other post-hysterectomoy subgroups and the general population ($p<0.05$).
Conclusion: The incidence of constipation after hysterectomy is high (22%). These patients have impaired QOL. Constipation after hysterectomy is not of the IBS-type, nor is hysterectomy a risk factor for developing IBS.

Cleansing of the colon: comparison of two PEG solutions and a sodium phosphate preparation.

R.J.F. Felt-Bersma, G. Kooyman, E.J. Kuipers. Dept of Gastro-enterology, Erasmus MC, Rotterdam.

A clean bowel is mandatory for a colonoscopy. Polyethylene glycol (PEG) preparations are increasingly used, but the 4-liter fluid intake is sometimes a problem. Sodiumphosfate solution requires less fluid intake (2,5 l), but can give electrolyte disturbances. In order to compare their cleansing ability and patient acceptance, two PEG solutions and a sodiumphosfate preparation were compared.
140 out-patients referred for colonoscopy were randomized for cleansing with 4 l Colofort® (PEG 4000), 4 l Klean prep® (PEG 3350) or 90ml Phosforal® (sodiumphosfate) with additional 2,5 l fluids. After cleansing, before colonocopy, the patients filled in a questionnaire concerning taste (1=awfull, 2=moderate, 3=normal, 4=good), abdominal cramps (1=very much, 2=much, 3=little, 4=none) and acceptance of the procedure (1=very poor, 2=poor, 3=moderate, 4=good). The endoscopist scored the effect of the cleansing on the colon and right hemicolon (1=very poor, 2=poor, 3=moderate, 4=good), as well as the endoscopic diagnosis.
Of the 140 patients, in 127 (50 m) mean age 51 y (18-96) all data could be obtained. Comparison for the three cleansing groups showed no difference for the subjective judgement of the patient concerning taste, abdominal cramps and acceptance. Objective blind scoring by the endoscopist for cleansing on the total colon showed a small difference (8%) towards a lesser clean colon with Phosforal® compared to Clean Prep® ($p=0.03$). No differences were found between Colofort® and Klean-prep®. Combining both PEG solution and comparing them with Phosforal® showed a tendency for less abdominal cramps ($p=0.07$) and a cleaner colon with PEG ($p=0.07$). Women had slightly more abdominal cramps and lesser acceptance. Colon surgery did not influence the results. Patients with diverticula were older, but no effect on cleansing was found.
Conclusion: The three bowel preparations for cleansing are comparable concerning their cleansing effect and acceptance by the patient

Diosgenin-induced biliary hypersecretion depends on the presence of Abcg8

A. Kosters[1], C. Kunne[1], N. Looije[1], F.Kuipers[2], S. B. Patel[3], A.K.Groen[1]. AMC Liver Center, Academic Medical Center, Amsterdam, The Netherlands[1], Dept of Pediatrics, University Hospital Groningen, Groningen, The Netherlands[2], Div of Endocrinology, Diabetes and Medical Genetics, Medical University of South Carolina, Charleston, SC, USA[3].

The heterodimer ABCG5/G8 has been shown to play a crucial role in biliary cholesterol (Ch) secretion. Our studies showed that the plant sterol diosgenin (D) induced a 16-fold increase in biliary Ch secretion in FVB mice without any change in hepatic Abcg5/g8 mRNA and protein expression, suggesting the activation of a parallel Ch secretory pathway. The existence this pathway was investigated by looking at the effect of dietary D on biliary Ch secretion in *Abcg8*$^{-/-}$ mice.
Abcg8$^{+/+}$, *Abcg8*$^{+/-}$ and *Abcg8*$^{-/-}$ mice were fed for 21 days either a control diet or the control diet with 1% diosgenin. Thereafter, the mice were cannulated via the gallbladder and bile was collected for 90 min. Subsequently, increasing concentrations of tauroursodeoxycholate (TUDC) were infused intravenously. Bile salts (Bs) and biliary lipids were determined using standard enzymatic techniques.
Biliary Ch secretion was 70% decreased in *Abcg8*$^{-/-}$ mice, whereas phospholipid (Pl) output was 30% and by 50% decreased in female and male *Abcg8*$^{-/-}$ mice, respectively. D did not affect basal bile flow, Bs and Pl secretion in *Abcg8*$^{+/+}$, *Abcg8*$^{+/-}$ and *Abcg8*$^{-/-}$ mice. In *Abcg8*$^{+/+}$ mice D induced Ch output 3-fold compared to *Abcg8*$^{+/+}$ mice fed the control diet. A similar increase in D-induced Ch secretion was observed in *Abcg8*$^{+/-}$ mice. In contrast, D failed to increase Ch secretion in *Abcg8*$^{-/-}$ mice both under basal conditions and during infusion of high concentrations of TUDC. Previously we have found that D increased hepatic expression of Oatp2, Hmg-CoA reductase and Egr1. D induced the expression of these genes also in *Abcg8*$^{-/-}$ mice. The kinetics of the D effect was investigated in *Abcg8*$^{+/+}$ and *Abcg8*$^{+/-}$ mice during infusion of TUDC. D strongly increased the affinity of Bs for Ch and had much less effect on maximal flux. Our results indicate that Abcg8 fully controls D-induced biliary Ch secretion and we speculate that D activates Abcg8 at the protein level.

The molecular mechanism of biliary cholesterol secretion

A. Kosters[1], C. Kunne[1], N. Looije[1], F. Kuipers[2], S.B. Patel[3], R.P.J. Oude Elferink[1], A.K. Groen[1]. AMC Liver Center, Academic Medical Center, Amsterdam, The Netherlands[1], Dept of Pediatrics, University Hospital Groningen, Groningen, The Netherlands[2], Div of Endocrinology, Diabetes and Medical Genetics, Medical University of South Carolina, Charleston, SC, USA[3].

Abcg5/g8 have been suggested to almost fully control biliary cholesterol (Ch) secretion. The proteins may directly flop Ch to the outer leaflet or serve a more indirect function, as proposed by Small (PNAS 100: 4-6, 2003). If the Abcg5/g8 heterodimer functions as a floppase, the outer leaflet of the canalicular membrane should be devoid of Ch in mice with impaired Abcg5/g8 function. In this study the kinetics of biliary Ch secretion in *Abcg8*$^{-/-}$ mice were investigated.
Abcg8$^{+/+}$, *Abcg8*$^{+/-}$ and *Abcg8*$^{-/-}$ mice were cannulated via the gallbladder and bile was collected for 90 min. Subsequently, increasing concentrations of tauroursodeoxycholate (TUDC) or taurodeoxycholate (TDC) were infused intravenously. Bile salts (BS) and biliary lipids were determined using standard enzymatic techniques.
Basal Ch secretion in *Abcg8*$^{-/-}$ mice was 70% reduced compared to *Abcg8*$^{+/+}$ mice. This rate did not decrease upon depletion of the endogenous BS-pool indicating BS-independency. Phospholipid secretion was about 50% decreased in *Abcg8*$^{-/-}$ mice. Intravenous infusion of TUDC enhanced biliary Ch secretion about 2-fold in *Abcg8*$^{-/-}$ to 0.6 ± 0.1 nmol/min/100g b wt. For comparison, in *Abcg8*$^{+/+}$ mice Ch secretion increased from 1.2 to 2.6 nmol/min/100g b wt, and *Abcg8*$^{+/-}$ mice showed intermediate levels. Infusion of the hydrophobic BS TDC in *Abcg8*$^{-/-}$ mice increased biliary Ch secretion to about 70% of the values in *Abcg8*$^{+/+}$. Interestingly, TDC infusion in *Abcg8*$^{+/-}$ led to complete normalization of Ch secretion, indicating a loss of rate control of Abcg8 on Ch secretion when hydrophobic BS are present. In conclusion, our data suggest that in the absence of Abcg8 the outer leaflet of the canalicular membrane still contains Ch. Hence, the mechanism proposed by Small may be correct and, rather than flopping, Abcg5/g8 may facilitate biliary Ch and perhaps phospholipid secretion as well.

FIC1 is expressed at the apical membranes of different epithelial cells in the digestive tract and is induced in the small intestine during postnatal development

S.W.C. van Mil[1,2], M.M. van Oort[2], I.E.T. van den Berg[2], R. Berger[2], R.H.J. Houwen[1], L.W.J. Klomp[2]. Dept of Pediatric Gastroenterology[1], and Dept of Metabolic and Endocrine diseases[2], University Medical Center, Utrecht.

Progressive familial intrahepatic cholestasis type 1 (PFIC1) and benign recurrent intrahepatic cholestasis (BRIC) are due to mutations in ATP8B1. ATP8B1 encodes FIC1, which is expressed in several tissues, most prominently in the intestine, pancreas and stomach and to a much lesser extent in the liver. In this study, FIC1 localization and expression during ontogeny was examined in healthy mice.
Immunoblot and RNA blot analysis indicated FIC1 is expressed abundantly in regions of the adult gastro-intestinal tract of humans and mice. Immunohistochemistry revealed that FIC1 was localized to the apical membranes of enterocytes, pancreatic acinar cells, gastric pit epithelial cells and hepatocytes and cholangiocytes. Subsequent analysis of early postnatal expression revealed that FIC1 expression in the small intestine was limited or absent at the age of 7 and 14 days and increased significantly with maturation. In contrast, pancreatic, hepatic and gastric FIC1 expression was not diminished during the first three weeks of postnatal development.
In conclusion, these data show that FIC1 is expressed in a tissue specific and developmentally-regulated fashion, suggesting a pleiotropic function at the apical membranes of epithelial cells. We speculate that the developing bile salt pool in the maturing intestine accounts for the increase in FIC1 protein expression in this tissue.

Intestinal bile salt absorption in mice with a mutation in the Fic1 gene

A. Groen[1], L. Kuik[1], K. Mok[1], C. Kunne[1], L. Bull[2], L. Agellon[3], W. Kramer[4], C. Paulusma[1], R. Oude Elferink[1]. Lab of Experimental Hepatology, AMC Liver Center, Academic Medical Center, Amsterdam[1], The Netherlands, Liver Center Laboratory, San Francisco General Hospital, University of California, San Francisco[2], California, USA, Dept of Biochemistry, University of Alberta, Edmonton, Alberta[3], Canada, DG metabolic Diseases, Aventis Pharma Deutschland GmbH[4], Germany.

Progressive Familial Intrahepatic Cholestasis type 1 (PFIC1) is caused by a mutation in the gene ATP8B1 (FIC1). This disease leads to progressive cholestasis.
FIC1 belongs to the P-type ATPase family and is proposed to function as an aminophospholipid flippase. The relation between this flippase function of FIC1 and the development of cholestasis in its absence remains unclear. A mouse model is available with the classic Byler mutation (G308V) in the murine orthologue Fic1. These animals do not suffer from cholestasis. Upon feeding a bile salt supplemented diet, they develop a sustained accumulation of serum bile salts, while canalicular bile salt secretion is normal. This points towards an alteration in intestinal bile salt absorption. Since the Ileal Bile Acid Transporter (IBAT) and Ileal Lipid Binding protein (ILBP) are thought to play a major role in bile salt absorption we looked at expression and function in the Ussing chamber model.
Ileal explants from wt and Fic1 mutant mice (strain 129Sv), both on control and 0,5% cholate diet displayed 10-fold higher bile salt transport than explants from colon or jejunum. Moreover, the transport in ileal explants was largely sensitive to the Ibat inhibitor BI-1, but no significant difference was observed in transport rates between control fed or bile salt wild type animals and Fic1 mutants.
We also examined Fic1 and Ibat protein expression throughout the ileum under different conditions by Western blotting. A significant variation was observed in Ibat expression among individual animals of the same genotype. In wt animals ileal Fic1 protein levels increased on the cholate diet. Both in wt and Fic1 mutant animals, there was no significant change in Ibat protein on a cholate diet.
These results demonstrate that there is no long term effect of bile salt feeding on the expression of Ibat; neither in wt nor in Fic1 mutants. We can not exclude however, that Fic1 mediates hyperacute regulation of Ibat activity in the ileum.

Highly effective enteral treatment of unconjugated hyperbilirubinemia in Gunn rats*

A.M. Hafkamp[1], R. Havinga[1], M. Sinaasappel[2], R.P.J. Oude Elferink[3], H.J. Verkade[1]. Dept Pediatrics[1], University Hospital Groningen, Groningen, Dept Pediatrics[2], Erasmus Medical Center, Rotterdam, Amsterdam Liver Center[3], Academic Medical Center, Amsterdam.

We aim to develop a treatment of unconjugated hyperbilirubinemia that is based on enteral administration, and has a higher efficacy than phototherapy (PT). In Gunn rats, dietary supplementation with calcium phosphate (CaP) or the lipase inhibitor orlistat (Orl) decreases plasma unconjugated bilirubin (UCB) levels. In Gunn rats, Orl is equally effective as PT. It is unknown whether effects of Orl and CaP are influenced by dietary fat content, and whether combined treatment (Orl+CaP) is superior to PT.
We determined in Gunn rats effects of Orl, CaP, and Orl+CaP on plasma UCB levels during a low-fat (LF) and high-fat diet (HF).
Gunn rats (4-5/group) were fed LF (15 energy% fat) for 3 wks, followed by HF (35 energy% fat) for 3 wks. Diets were not supplemented (controls), or supplemented with Orl (200 mg/kg chow), CaP (20 g/kg chow), or Orl+CaP. Separate Gunn rats on HF received continuous PT (9 μW/cm²/nm) for 2 wks. Plasma UCB levels and fecal fat excretion (72h) were determined by HPLC and GC.
In all rats, except CaP-supplemented, plasma UCB decreased profoundly by the change from LF to HF ($p<0.01$). In controls, plasma UCB decreased from 248±31 to 135±10μM (LF/HF; $p<0.001$), and appeared inversely correlated with fecal fat excretion (LF: 0.07±0.03; HF: 0.74±0.12 mmol/24h; $r=-0.96$, $p<0.001$). During either diet, Orl or CaP decreased plasma UCB compared with controls (LF: Orl-30%, $p<0.05$, CaP-40%, $p<0.001$; HF: Orl-28%, $p<0.01$, CaP-21%, NS). Orl+CaP induced the most profound decrease (LF:-54%, HF:-44%; $p<0.01$). Orl+CaP was more effective than either CaP (LF/HF) or Orl (LF)($p<0.05$), and than PT (final plasma UCB, Orl+CaP: 76±7; PT: 97±10μM; $p<0.01$).
Conclusions: Plasma UCB levels in Gunn rats are inversely related to dietary fat content. Dietary supplementation with Orl+CaP profoundly decreases plasma UCB levels and is more effective than PT. Present results strongly support the feasibility of a highly effective enteral treatment of patients with unconjugated hyperbilirubinemia.

Extensive chimerism in liver transplants: vascular endothelium, bile duct epithelium and hepatocytes

W.R. ten Hove[1], B. van Hoek[1], I.M. Bajema[2], J. Ringers[3], J.H.J.M. van Krieken[4], E.L. Lagaaij[2]. Dept of Gastroenterology and Hepatology[1], Dept of Pathology[2] and Dept of Surgery[3], Leiden University Medical Center, Dept of Pathology[4], University Hospital Nijmegen.

The transplanted liver has been shown to be particularly capable of inducing tolerance. An explanation may be the presence of chimerism. Cells of donor origin have been found in recipient tissues after transplantation of any solid organ. Evidence for the presence of cells of recipient origin within the transplanted liver is very limited. We investigated whether non-lymphoid cells of recipient origin can be found within human liver allografts.
Five male patients who received a liver transplant from a female donor and 11 patients who received an HLA-I mismatched liver transplant were studied. We confirmed our observations with two different techniques in combination with double staining techniques. To identify male cells in female liver transplants, we used in-situ hybridization for sex chromosomes. To identify specific HLA class-I antigens of recipient origin we used immunohistochemistry with HLA-class I specific antibodies. Double staining was done to discriminate different cell lineages and inflammatory cells. Endothelial cells of recipient origin were found in 14 out of 16 donor livers. Bile duct epithelial cells of recipient origin were found in five out of 16 cases. Hepatocytes of recipient origin were only seen in one out of the five studied sex-mismatched donor livers.
Conclusions: Our study provides evidence that cells of recipient origin can replace biliary epithelial cells, endothelial cells and hepatocytes within the human liver allograft. This is consistent with the concept that circulating pluripotent progenitor cells exist, capable of differentiating into endothelial cells, epithelial cells and hepatocytes.

Intensive screening methods detect early diffuse lesions in hereditary diffuse gastric cancer (HDGC)

J.H.F.M de Bruin[1], F.M. Nagengast[2], J. Bonenkamp[3], J.H.J.M. van Krieken[1]. Dept of Pathology[1], Gastroenterology[2], Surgery[3], University Medical Centre St. Radboud, Nijmegen.

Hereditary diffuse gastric cancer (HDGC) is caused by germline truncating mutation in E-cadherin (CDH1) gene in 30% of cases. HDGC is autosomal dominant inherited and gene carriers have a high predisposition to develop diffuse gastric cancer of signet ring celtype, predominantly at young age. Screening for this type of cancer in early stages is extremely difficult, because of time-consuming mutation analysis and a high false-negative rate of endoscopic biopsies. However, we recently encountered a HDGC family, in whom signet ring cell cancer was diagnosed after multiple gastric biopsies in two female siblings (27 and 29 years of age), who proved to be gene carriers. We searched for early morphological changes in the gastric mucosa and subsequent genetic defects to improve the early diagnosis of this often fatal disease.
Microscopically we observed an intramucosal precursor lesion. In the gastric pits cells appearing like signet ring cells were present, within the contours of the glands which are somewhat distorted. E-cadherin staining was retained and maybe as a consequence they remain cell to cell adhesion. This new finding requires pathological expertise, but is of great help in early diagnosis of diffuse gastric cancer in gastric biopsies. After total gastrectomy extensive diffuse gastric signet ring cell cancer was found in both patients. The intramucosal precursor lesions were only observed in the two gene carrying siblings and was absent in a non-gene carrier sibling.
Sequencing analysis of E-cadherin gene in this family revealed the presence of a heterozygous splice-site (truncating) mutation in exon 8 in both the gene carriers, which has not previously been described.
In conclusion endoscopic screening with multiple biopsies in suspected HDGC families can reveal early intramucosal signet ring cells, which are probably markers of the presence of diffuse gastric cancer. This finding can have important implications in screening family members in HDGC.

Clinical application of video capsule endoscopy in 70 consecutive patients

S.A.C. van Tuyl[1], M.F.J. Stolk[1], R. Timmer[1], E.J. Kuipers[2]. Depts of Gastroenterology, St. Antonius Hospital Nieuwegein[1] and Erasmus MC University Medical Center Rotterdam[2].

Video capsule endoscopy (VCE) is a new tool to investigate the small bowel. The most important indication is anemia due to gastrointestinal blood loss. Technical improvements like automatic red detection are recently developed to improve diagnostic yield and reduce reading time.
To assess technical feasibility, diagnostic yield and clinical impact of VCE, 70 procedures were performed in a heterogeneous patient population. After a 12 hour fast, patients swallowed the Given Imaging videocapsule. Findings were considered diagnostic if the observed finding could explain the signs/symptoms of the patient and helped plan further management. Findings were considered suspicious if an observed finding failed to completely explain the signs/symptoms of the patient.
Seventy patients (36 male/34 female) were studied. Mean age was 56.0±18.0 (sd) years (range:17-84 years). Main indications were anemia and a history of gastrointestinal bleeding (79%), suspicion of small bowel inflammatory disease (10%) and diarrhea (6%). Mean video viewing time was 53±14 minutes. The cecum was reached in 50 (71%) patients. No bowel obstruction occurred. In three patients capsules were temporarily retained in stomach and colon. Mean gastric transit time was 34±42 (sd) min. Small intestinal transit time was 247±84 min.
A definite diagnosis was made in 22 (31%) patients. Suspicious findings were found in 31 (44%) patients. No diagnosis was found in 19 (27%) patients. Diagnosis were angiodysplasia (23%), small bowel inflammation (17%), active bleeding (9%), Rendu-Osler-Weber disease (9%) and tumor (4%). Interestingly, in 8 (11%) patients gastric abnormalities were found. VCE diagnosis led to a significant change in clinical management in 31 (44%) patients. Automatic red detection was correct in 67% of patients.
Conclusions: VCE is an important diagnostic tool with a high diagnostic yield and a considerable clinical impact in a heterogeneous patient population.

Narrow-band imaging improves mucosal pattern recognition in Barrett's oesophagus

M. Kara[1], M. Ennahachi[1], F. Ten Kate[2], P. Fockens[1], S. Van Deventer[1], J. Bergman[1]. Dept of Gastroenterology and Hepatology[1], Dept of Pathology[2], Academic Medical Center, Amsterdam.

Mucosal patterns in Barrett's oesophagus (BE) can only be detected with high-resolution endoscopy (HRE) combined with chromoendoscopy. Narrow-Band Imaging (NBI) is a new real-time endoscopic technique that enhances the visibility of the mucosal surface structure without the use of staining agents. The aims of this ongoing study is to compare HRE alone and HRE with NBI in the detection of mucosal patterns in BE, to classify these patterns and to determine the correlation of mucosal patterns to histopathology. NBI is based on the fact that the depth of light penetration is wavelength dependent; the shorter the wavelength the shallower the penetration. The prototype NBI-unit (Olympus Tokyo, Japan) uses a RGB-sequential endoscopy system consisting of a NBI-filter with narrowed RGB-band pass-ranges, increased relative contribution of blue light, and diminished contribution of red light. The system uses a high resolution video endoscope (GIFQ240 Zoom-NBI) and is equipped with both a standard HRE-mode and a HRE-NBI-mode, with the possibility of switching between both modes. Patients with a known BE underwent endoscopy using this unit; magnified still images of mucosal areas were taken with HRE alone and HRE with NBI, respectively and biopsies were taken for histological correlation. Using visual analogue scales, mucosal patterns detected by HRE with NBI were found to be superior over patterns detected by HRE alone. Moreover, detected patterns could be classified into two main categories: regular (circular, oval or longitudinal) and irregular patterns (irregular villi/loops or destructed pattern).
Conclusion: NBI improves mucosal pattern detection in BE without the need for chromoendoscopy. Future studies will elucidate the correlation between mucosal patterns and histopathology, and the clinical relevance of the improved mucosal contrast seen by NBI.

A randomized cross-over study comparing Light-induced Fluorescence Endoscopy LIFE) with Standard Video-Endoscopy SE) for detection of early neoplasia in Barrett's Esophagus (BE)

M. Kara, W. Rosmolen, M. Smits, P. Fockens, G. Tytgat, J. Bergman. Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam.

LIFE is a novel imaging technique that allows real-time endoscopic detection of dysplasia based on differences in tissue autofluorescence. The aim of this prospective randomized cross-over study was to compare LIFE with SE in the detection of high-grade dysplasia and early cancer (HGD/ca) in BE. 47 patients (35males, mean age 64±12.3yrs) known with BE, referred for surveillance (n=29) or work-up of endoscopically invisible HGD/ca (n=18) underwent endoscopy using the prototype LIFE-II-system (Xillix Corp, Richmond, Canada), which uses a fiber-optic endoscope and an overhead camera that enables switching between SE and LIFE. Patients were randomized to LIFE or SE as the first procedure followed by cross-over to the other technique after 6 weeks. Procedures were performed by 2 experienced endoscopists who were allocated to the first procedure before randomization. The second endoscopist was blinded to findings at the first endoscopy. Two biopsies were taken from all visible lesions followed by random biopsies (Seattle protocol). Pathologists were blinded to the imaging technique used. After the 2 procedures 24 patients had no dysplasia, 8 low-grade dysplasia (LGD) and 15 HGD/ca. LIFE misdiagnosed 3 of the 15 (20%) cases with HGD/ca as having LGD, while SE misdiagnosed other 3 as having indefinite for dysplasia (n=2) and no dysplasia (n=1).

	LIFE (n=47)	SE (n=47)	
Mean number of Bx	12.2±6.24	11.5±6.48	p=0.36
Mean duration endoscopy (min)	22±8.1	20±11.6	p=0.12
Nr of focal lesions identified	44 in 24 pts	27 in 17 pts	p=0.21
Nr of these lesions with HGD/ca (specificity)	17/44 (39%)	14/27 (52%)	p=0.40
Pts with HGD/ca (sensitivity, targeted Bx only)	10/15 (67%)	9/15 (60%)	p=0.79
Pts with HGD/ca (sensitivity, targeted+random Bx)	12/15 (80%)	12/15 (80%)	p=1.00

In this study LIFE failed to improve the detection of HGD/ca in BE. Both LIFE and SE missed HGD/ca in 20% of patients.

E**ndoscopic mucosal resection (emr) for high-grade dysplasia (hgd) or early cancer (ec) in barrett's esophagus (be)**

J. Bergman[1], F. Peters[1], W. Rosmolen[1], B. Bultje[2], P. Fockens[1], J. van Lanschot[3], F. ten Kate[4], S. van Deventer[1], G. Tytgat[1]. Depts of Gastroenterology[1], Clinical Epidemiologyand Biostatistics[2], Surgery[3], Pathology[4], Academic Medical Center, Amsterdam.

Aim was to prospectively evaluate EMR for the removal of HGD/EC in selected BE patients.
BE patients with a revised histological diagnosis of HGD/EC underwent standard endoscopy, fluorescence endoscopy, and EUS. Patients with focal abnormalities <2 cm or >2 cm and major contraindications for surgery were included. EMR was performed with a flexible large calibre cap (OD 19 mm) after lifting with adrenaline solution.
There were 41 patients (m/f: 31/10; mean age: 66±8.9 yrs), with 6 type I, 5 IIa, 6 IIb, and 24 IIa/IIc lesions. 19 Patients had lesions >2 cm and underwent piecemeal resection (median no. of EMRs: 2; range 2-5). Complications occurred in 15 patients (37%): 13 bleedings during endoscopy, managed by clipping/injection (classified “mild”) and 2 perforations (one symptomatic classified “severe”, one asymptomatic classified “moderate”). No patient had signs of rebleeding or required blood transfusions. The perforations (both piecemeal) were treated conservatively with full recovery. No complications were seen after 24 hrs or 30 dys f-u. Specimens had a mean diameter of 22.3±1.09 mm, all involved the submucosa. Histology showed no dysplasia in 3, HGD in 12, T1m in 18 and T1sm in 8 patients. The lateral resection margins could not reliably be assessed in 19 patients with piece meal resections. Of the other 22 patients, 4 had lateral margins free of HGD/EC. Of 8 patients with T1sm, deeper resection margins were positive in five. After EMR, five patients underwent surgery. The remaining 36 patients underwent endoscopic f-u (6), additional EMR (9), or ablative therapy with PDT (18) or APC (3).
Conclusions: EMR is associated with complications in a considerable number of patients but most complications are mild and easily managed. In this group of patients, EMR with a large calibre cap resulted in complete resection in only 10%. For complete eradication of HGD/EC additional endoscopic treatment (e.g. PDT or widespread EMR) is necessary in most cases.

5-Aminolevulinic Acid Photodynamic Therapy versus Argon Plasma Coagulation for Ablation of Barrett's Esophagus: A Randomized Trial

M. Hage[1,2], P.D.Siersema[1], H. van Dekken[2], E.W. Steyerberg[3], J. Haringsma[1], W. v.d. Vrie[1], T.E Grool[1], R.L.P. van Veen[4], H.J.C.M. Sterenborg[4], E.J. Kuipers[1]. Depts of Gastroenterology & Hepatology[1], Pathology[2], Public Health[3] and Radiation Oncology (Photodynamic Therapy and Optical Spectroscopy Programme)[4], Erasmus MC University Medical Center Rotterdam.

Currently, both photochemical and thermal methods are used for ablating Barrett's esophagus (BE). The aim of this study was to compare 5-aminolevulinic acid induced photodynamic therapy (ALA-PDT) with argon plasma coagulation (APC) with respect to complete reversal of BE. Two different ALA-PDT treatment schemes were used: (a) a single dose of 100 J/cm2 (PDT1x100J-group; n=13), and (b) a fractionated dose of 20 and 100 J/cm2 (PDT20+100J-group; n=13). APC was performed at 65 W in 2 sessions (APC-group; n=14). If complete elimination of BE was not achieved by the designated treatment at 6 weeks, then the remaining area of BE was ablated by additional APC. All patients received proton pump inhibitors.
Median follow-up was 12 months. Median BE length before treatment was 3 cm in all groups (32 no dysplasia and 8 low-grade dysplasia). Mean endoscopic reduction of BE at 6 weeks was 51% (range, 20-100) in the PDT1x100J-group, 86% (range, 0-100) in the PDT20+100J-group, and 93% (range 40-100) in the APC-group (PDT1x100J vs. PDT20+100J or APC: $p<0.005$) with histologically complete ablation in 1/13 (8%) of the PDT1x100-group, 4/12 (33%) of the PDT20+100J-group and 5/14 (36%) of the APC-group (p=NS). Remaining BE was treated by APC in 23/40 (58%) patients. Histological examination at 12 months revealed complete ablation in 9/11 (82%) patients of the PDT1x100J-group, in 9/10 (90%) patients of the PDT20+100J-group and in 8/12 (67%) patients of the APC-group (p=NS). At 12 months, no dysplasia was detected. Side effects, i.e. pain, nausea and vomiting and mild transient increase in liver transaminases were more common after PDT than APC. One patient died 3 days after treatment with fractionated PDT, presumably from cardiac arrhythmia.
Conclusions: ALA-PDT in combination with APC is slightly more effective than APC alone in reversing Barrett's epithelium to squamous epithelium. However, treatment with ALA-PDT is accompanied by more side effects.

Self-expanding metal stents with anti-reflux valve for the prevention of gastroesophageal reflux: a randomized trial

M.Y.V. Homs[1], P.J. Wahab[2], E.W. Steyerberg[3], J. Haringsma[1], T.A. Grool[1], E.J. Kuipers[1], P.D. Siersema[1]. Dept of Gastroenterology & Hepatology[1] and Public Health[3], Erasmus MC / University Medical Center Rotterdam, Dept of Gastroenterology[2], Rijnstate Hospital Arnhem.

When deployed across the gastroesophageal junction, self-expanding metal stents can predispose to gastroesophageal reflux. Recently, metal stents have been developed that have a distal extension of the coating to form a windsock-type valve. Our aim was to study the effectiveness of the FerX-Ella stent (Ella-CS, Czech Republic) with anti-reflux valve (length of valve: 47 mm) in preventing gastroesophageal reflux in patients with carcinoma of the distal esophagus and gastroesophageal junction. Between April 2002 and May 2003, 30 patients were randomized to receive a FerX-Ella stent with anti-reflux valve (n=15) or a standard open FerX-Ella stent (n=15). Patients were followed prospectively for clinical outcome and were asked to undergo 24-hour pH-monitoring at 14 days after treatment.
Dysphagia improved similarly in patients treated with anti-reflux or open stents from a median of 3 (liquids only) to 1 (eat some solid food) ($p<0.001$). Reflux symptoms were reported by 3/12 (25%) patients with an anti-reflux stent and by 2/14 (14%) patients with an open stent (p=NS). Esophageal acid exposure time was abnormal in both stent groups (mean total reflux time: anti-reflux (n=9): 25.3% vs. open (n=2): 9.5% (normal: <4%); median number of reflux episodes >5 minutes: anti-reflux: 14 vs. open: 5 (normal: <1)). Major complications were not different between patients with or without an anti-reflux stent (3/15 (20%) vs. 2/15 (13%)), and consisted of bleeding (n=2), severe pain (n=2), and aspiration pneumonia (n=1). The main cause of recurrent dysphagia was stent migration in 5/30 (17%) patients. Median survival was similar in both patient groups (138 versus 107 days).
Conclusions: The FerX-Ella stent provides good symptomatic relief against malignant dysphagia, however its anti-reflux valve does not prevent gastroesophageal reflux. The main reason for this might be the relatively short length of the valve, still allowing gastroesophageal reflux to occur.

Good palliation with Self-Expanding Metal Stents (SEMS) for malignant obstruction of the colon: a five-years experience

R.J.I. Bosker[1], F. ter Borg[2], E.H. Eddes[1], M.M.J.J.R. Jaspers[3], M. Eeftinck Schattenkerk[1]. Dept. of Surgery[1], Gastroenterology[2] and Radiology[3], Deventer Hospital.

Palliation of incurable patients with malignant colon obstruction is traditionally achieved by a surgical colostomy. This procedure requires general anaesthesia and bears the risk of prolonged admission due to slow recovery and co-morbidity. Furthermore, a colostomy has a negative impact on quality of life which is undesirable given the dismal prognosis.
Since 1993 SEMS have been increasingly used to palliate such obstructtions, with publication of some small series. We report our five-years experience with SEMS.
From 1997 to 2002 we treated 26 patients having incurable malignant colon obstruction with SEMS. SEMS were placed in a day-care setting without general anaesthesia. In thirteen patients, SEMS were placed radiologically (often with endoscopic assistance), in the others it was done endoscopically with radiological assistance.
The study group consisted of 17 men and 9 women. Mean age was 71 (46-94) years. The malignant obstruction was located in the rectum (6x), sigmoid (16x), descending (2x) or transverse colon (2x).
In 21 cases the obstruction was caused by a colorectal carcinoma, in 4 cases it was due to external compression (2x stomach cancer, 1x ovarian cancer, 1x carcinoid). In one case, an ischemic stricture in the sigmoid was treated with a SEMS because the patient was considered unfit for surgery.
During follow-up, the SEMS dislodged in five case. In three of these cases, a new SEMS was placed successfully, in the other patients it was decided to perform a colostomy.
One patient developed a perforation of the rectal wall during SEMS placement, which was treated with an urgent colostomy.
At present, three patients are still alive, twenty-three have died without signs of obstruction. Mean survival was 128 (2-420) days .
We conclude that SEMS is a valuable alternative to surgical colostomy for the treatment of malignant colonic obstruction in incurable patients. Before proceeding to a surgical intervention, SEMS placement should be considered.

Genetische factoren bij anusatresie
Presentatie MLDS-project door de heer prof. dr. H.G. Brunner - UMC St Radboud Nijmegen.

Little is know about the genetic causes that underlie anal atresia in humans. Evidence gleaned from patients with large structural chromosomal abnormalities suggests that a gene or genes on chromosome 13 may be involved. Many patients with chromosome 13 deletions involving band q32 have anal atresia. Other regions of interest were on chromosome 10 (which is homologous to the localization of a mouse mutant for anal atresia), and chromosome 21 (because of the increased risk of patients with Down syndrome for anal atresia). We used DNA markers that detect polymorphisms to scan for small deletions and duplications in a cohort of 40 Dutch patients with anal atresia. A total of 20 such markers were investigated on chromosome 13 (8 markers), on chromosome 10 (5 markers), and across chromosome 21 (7 markers). All results were normal.
It is possible that the genetic factors that influence anal atresia are located on other chromosomes. It is equally likely, that any abnormalities in this cohort of patients were below the level of resolution of the techniques that were used. We have subsequently developed a new technique for the submicroscopic analysis of the chromosomes. This can be tested in the future on the DNA material of this group of patients.

High homocysteine levels, and not vitamin B12 deficiency, increase the risk of ischemic relapse and mortality.

F. Vlemmix, M.G.H. van Oijen, R.J.F. Laheij PhD, L. Paloheimo, J.B.M.J. Jansen MD PhD, F.W.A. Verheugt MD PhD. Dept of Gastro-enterology and Cardiology, UMC St Radboud, Nijmegen.

Malabsorption of dietary vitamin B12 leads ultimately to an increase in circulating total homocysteine (tHcy) levels. An elevated plasma tHcy level is an independent and graded risk factor for cardiovascular disease (CVD). Gastritis caused by Helicobacter pylori (Hp) infection leads to malabsorption of dietary vitamin B12 and may be a risk factor for developing a CVD. The aim of this study was to determine the association between vitamin B12 and tHcy levels, Hp serology and CVD-related morbidity and mortality in patients with cardiovascular disease.
Overall 229 study subjects were recruited in the first five months of 1998. Serum vitamin B12, plasma tHcy levels and Hp serology were measured in fasting blood samples. Patient characteristics, medical information and the pre-existence of cardiovascular risk factors were assessed. Patients were followed for the next five years and the prevalence of CVD related mortality and morbidity were collected from medical files and by interview.
In the period of five years, 48 (21%) of the patients experienced a cardiovascular event and 14 (6%) died from CVD. There was no difference in survival between the patients with a high (≥ 339 ng/l) or a low vitamin B12 level and an ischemic heart disease (IHD) at baseline (p=0.21). Patients with hyperhomocysteinemia (>16 µmol/l) and an IHD at baseline had an increased risk of a secondary cardiovascular event (p=0.05), with an hazard ratio of 2.22 (95% CI :1.40-3.04) in comparison to those with a normal plasma tHcy levels and an IHD at baseline. There was no correlation found between decreased serum vitamin B12 and elevated tHcy levels (p=0.63) or between vitamin B12 and Hp serology (p=0.11).
In conclusion, the results of this study showed that a high plasma tHcy level, and not a low serum vitamin B12 level leads to an increased risk of CVD-related morbidity and mortality in patients with an IHD at baseline. Infection with Hp did not influence this risk.

LapBand vs. open VBG, a prospective randomized trial

F.M.H. van Dielen[1], PB Soeters[1], GAPG van Mastrigt[2], JWM Greve[1].
Dept of General Surgery[1], Dept of Clinical Epidemiology and Medical Technology Assessment[2], University hospital of Maastricht.

Morbid Obesity is a major problem in western society and carries considerable co-morbidities. Laparoscopic adjustable gastric banding (LAGB) and open vertical banded gastroplasty (VBG) are treatment modalities for morbid obesity. However, up till now no prospective randomised clinical trial (RCT) has been performed to assess the long-term-effectiveness of LAGB compared to open VBG. For this reason a RCT has been performed in our hospital.
From May 1999 till December 2001 100 patients were included in the study. 50 patients underwent VBG and 50 LAGB. Age and sex were comparable. Outcomes included length of hospital stay (LHS), direct postoperative complications, percent excess weight lost (%EWL), change in BMI, reduction in total co-morbidities and long-term complications.
Mean preoperative BMI (VBG/LAGB) was 46.4/46.7, total co-morbidities 1.3/1.3. LHS was significantly shorter in the LAGB group (3.5 vs. 6.8 days). Three LAGB were converted to open, 1 to gastric bypass.
Directly after VBG, in 3 patients relaparotomies were performed due to leakage. 2 of these patients died (4%) compared to 0 in the LAGB group (NS). After 1 year, decreased BMI and %EWL were significantly better in the VBG group compared to the LAGB group (72.7% and 30.7 kg/m² vs. 53.3 and 35.0 resp.). Total co-morbidities significantly decreased and did not differ. Within a median of 2 years after LAGB, 20 patients needed revisional surgery due to pouch dilation/slippage (n=13), band leakage (2), erosion (2) or access port problems (3). In the VBG group 16 patients needed revisional surgery due to staple line disruption (14) or to narrow outlet (2). Eight patients developed a hernia cicatricalis in the VBG group.
This RCT demonstrates that despite the initial better weight loss in the VBG group, based on complication rates and clinical outcome, LAGB and VBG are equally effective in treatment of morbid obesity. However, after LAGB the LHS is shorter and no hernia cicatricalis will develop.

The cholinergic anti inflammatory pathway regulates host defense during septic peritonitis in mice

D.J. van Westerloo[1], J. Winkelhagen[2], J. Daalhuisen[1], M.J. Bruno[3], K.J. Tracey[4], A.F. de Vos[1], S. Florquin[5] and T. van der Poll[1]. Depts of Experimental Internal Medicine[1], Surgery[2], Gastroenterology[3] and Pathology[5], AMC Amsterdam, Netherlands, Lab of biomedical sciences[4], North shore Long Island Jewish research institute, NY, USA.

The nervous system, through the vagus nerve, can downregulate inflammation by decreasing the production of TNF-α by macrophages during experimental endotoxemia. The effects are carried out by cholinergic nicotine receptors on macrophages(Tracey, Nature 2003).
We evaluate the role of this “cholinergic anti inflammatory pathway” during septic peritonitis in mice. Peritonitis was induced by intraperitoneal injection with 5*104 CFU E.coli, mice were euthanized 24 hours postinfection. Peritonitis was preceded by either inhibition of the cholinergic anti inflammatory pathway by unilateral cervical vagotomy or stimulation of this pathway by pretreatment of mice with nicotine.
Previous cervical vagotomy resulted in an enhanced influx of neutrophils to the peritoneal cavity, higher levels of pro inflammatory cytokines in peritoneal lavage fluid (PLF) and a marked increase in liver necrosis in response to peritonitis. Nicotine pretreatment strongly decreased bacterial clearance during septic peritonitis. Cell influx and pro inflamematory cytokine levels in PLF were all lower in these animals. Liver necrosis was significantly ameliorated whereas survival was impaired.

Inhibition of the cholinergic anti inflammatory pathway induces a pro inflammatory state whereas stimulation of the cholinergic anti inflamematory pathway strongly decreases host defense by inhibition of the production of pro inflammatory cytokines during septic peritonitis. These data provide the first evidence for an important role of this pathway in regulating host defense during infection.

Versatile roles for Bone Morphogenetic Protein in gut development and gastric cancer

S.A. Bleuming, G.R. van den Brink[1], S.J.H. van Deventer[2], M.P. Peppelenbosch[1]. Dept of Experimental Internal Medicine[1], and Dept of Gastroenterology[2], Amsterdam Medical Center, Amsterdam.

The embryonic development of the vertebrate gut requires signaling between the endoderm and mesoderm for establishing its normal anterior posterior (AP) axis and for tissue-specific differentiation. One of the main factors implicated in these embryonic events in the formation of the gut include Bone Morphogenetic Protein (BMP).
We have investigated the roles of BMP in stomach, its involvement in gastric inflammation and in gastric cancer.
We assessed BMP receptor expression in stomach cell lines using RT-PCR and immunoblotting. We investigated the effects of recombinant BMP2 on stomach cell lines using immunoblotting for markers of differentiation, proliferation, and apoptosis. We studied the expression of BMP2, its receptors and signal transduction elements in vivo in mouse and human stomach tissue using immunohistochemistry. We also determined the effect of the BMP antagonist noggin in vivo in mice by assessing stomach tissue with immunohistochemistry.
BMPRIa, BMPRIb, and BMPRII are all expressed in stomach epithelial cell lines. BMP2 inhibits cell growth by inhibiting proliferation and promoting differentiation and apoptosis. BMP2, BMPRIa, BMPRIb, BMPRII, PSmad1, and Smad4 are expressed in stomach epithelium in a gradient pattern. BMP2 is highly expressed in the infiltrate in of inflammation in human stomach epithelium. The gradient pattern of PSmad1 expression is lost in inflamed stomach epithelium, which is due to the high expression of BMP2 in the infiltrate. In analogy with the involvement of BMP in gut development is the BMP pathway also involved in the continuous renewal (a homeostasis of proliferation and differentiation) of stomach epithelium in the adult phase. Our results show that molecular changes in the expression pattern of the BMP signaling forms the basis of the morphological changes in the stomach prior to the neoplastic deformation, which can lead to stomach cancer.

Nickel-responsive induction of urease activity is restricted to gastric Helicobacter species

A.H.M. van Vliet, J. Stoof, E.J. Kuipers and J.G Kusters. Erasmus MC, Rotterdam.

The nickel-cofactored urease enzyme is an essential virulence factor of the human gastric pathogen *Helicobacter pylori*, as its enzymatic activity provides protection against low pH. This protective function is dependent on nickel- and acid-responsive induction of urease activity. The presence of the urease enzyme is not restricted to *H. pylori*, but extends to all known gastric Helicobacter species, and to some but not all non-gastric *Helicobacter* species. The aim of this study was to determine whether nickel-responsive induction of urease activity extends to other gastric and non-gastric *Helicobacter* species. The gastric Helicobacter species *H. pylori*, *H. acinonychis* and *H. mustelae*, and the non-gastric *Helicobacter* species *H. hepaticus* and *H. bilis* were grown in Brucella or BHI media supplemented with 10% serum and 100 µM $FeCl_3$. Media were supplemented with $NiCl_2$ to final concentrations of 0-1000 µM, and urease activity was measured using a colorimetric assay. Urease activity was generally higher in the gastric Helicobacters when compared to the non-gastric Helicobacters. *H. mustelae* and *H. acinonychis* demonstrated nickel-responsive induction of urease activity to similar levels as *H. pylori*. In contrast, urease activity was nickel-independent in *H. hepaticus* and *H. bilis.* Urease activity in the gastric *Helicobacter* species was dependent on the medium used, as urease activity was higher in gastric *Helicobacter* species in the nickel-rich BHI medium when compared to the nickel-restricted Brucella media, whereas such a difference was not apparent in the non-gastric *Helicobacter* species.
Conclusion: Nickel-responsive induction of urease activity seems to be an adaptive response specific for gastric *Helicobacter* species.

Detection of high-level tetracycline resistance in Helicobacter pylori using PCR-RFLP

M.M. Gerrits[1], M.L. Ribeiro[2], M. Berning[1], E.J. Kuipers[1], S. Mendonça[2], A.H.M. van Vliet[1], J. Pedrazzoli Jr.[2] and J.G. Kusters[1]. Dept of Gastroenterology and Hepatology[1], Erasmus MC-University Medical Center Rotterdam, The Netherlands, Clinical Pharmacology and Gastroenterology Unit[2], São Francisco University Medical School, Bragança Paulista, SP, Brazil.

Tetracycline-based therapies are highly effective for the treatment of *Helicobacter pylori* infections, but currently the incidence of tetracycline resistance is increasing. High-level tetracycline resistance in *H. pylori* is restricted to the occurrence of specific mutations at positions 926-928 of both 16S rRNA genes. In this study a molecular-based PCR restriction fragment length polymorphism (PCR-RFLP) was developed for the detection of high-level tetracycline resistance in *H. pylori*. Genomic DNA of high-level tetracycline-resistant (Tet^R), low-level Tet^R mutants and tetracycline-sensitive (Tet^S) *H. pylori* isolates was amplified using *H. pylori* specific 16S rRNA primers and digested with the restriction enzyme *Hin*fI.
(5'-G/ANTC-3'). This enzyme digests the previously described mutation mediating high-level tetracycline resistance (AGA-TTC), but not that of Tet^S or low-level Tet^R isolates. As predicted by sequence analysis, the PCR fragments derived from the six high-level Tet^R *H. pylori* isolates were digested into three fragments, while the digestion of the PCR fragments of the low-level Tet^R mutants and the Tet^S strains revealed only two fragments. In conclusion, the PCR-RFLP approach described here allows for rapid detection and discrimination of the clinically relevant Tet^R *H. pylori* isolates. This method can be applied to gastric biopsy specimens, allowing the detection of high-level Tet^R *H. pylori* isolates without the need for culture and within a day after endoscopy.

B-cells produce immunoregulatory molecules in both HLA-B27 rats with colitis and non-transgenic littermates

F. Hoentjen[1,2], S.L. Tonkonogy[3], R. Balfour Sartor[2], C.J. Mulder[1] and L.A. Dieleman[2]. Dept of Gastroenterology[1], Vrije Universiteit Amsterdam, The Netherlands, Center for Gastrointestinal Biology and Disease[2], University of North Carolina at Chapel Hill, Chapel Hill, USA,College of Veterinary Medicine[3], NC State University, Raleigh, USA.

HLA-B27 transgenic (TG) rats develop spontaneous colitis when colonized by specific pathogen-free (SPF) intestinal bacteria. We reported previously that HLA-B27 TG mesenteric lymph node cells (MLN) stimulated with cecal bacterial lysate (CBL) produce more IFN-γ and IL-12 compared with MLN from non-TG littermates, whereas non-TG MLN cells produce significantly more IL-10. Therefore, the aim of this study was to compare production of the immunoregulatory molecules TGF-β and PGE_2 in TG vs. non-TG MLN cells after physiologic stimulation with CBL.
MLN cells isolated from 4 month old germ-free (GF) and SPF HLA-B27 TG rats and non-TG littermates were depleted of T or B cells by negative selection using pan-T cell- or CD45RA antibody-coated magnetic beads, respectively. Both unseparated and fractionated MLN cells were stimulated with various doses of CBL (1-100 µg/ml) from non-TG rats. Supernatants were collected at 3 or 5 days, TGF-β and PGE_2 levels were determined by ELISA.
SPF non-TG MLN cells stimulated with CBL produced significantly more TGF-ß than those from TG rats (non-TG: 612 ± 85, TG: 221 ± 48 pg/ml,γP<0.01), whereas PGE_2 levels did not differ. B cell depletion almost totally abrogated TGF-β production in SPF non-TG and TG MLN cells (non-TG: 37 ± 7, TG: 29 ± 23 pg/ml, P<0.01 vs. unseparated MLN cells), however T cell depletion had no effect compared to unfractionated MLN cells. GF non-TG MLN cells produced more TGF-β than TG MLN cells when stimulated with CBL 100 µg/ml (non-TG: 644 ± 4, TG: 370 ± 11 pg/ml, P<0.01). However, when GF MLN were stimulated with CBL 10 µg/ml, there was no significant difference in TGF-β production.

In vitro intestinal intercellular adhesion molecule-1 (ICAM-1, CD54) expression is decreased by the n-3 PUFA eicosapentaenoic acid (EPA)

J.D. Ramakers, R.P. Mensink, J. Plat. Dept of Human Biology, Maastricht University, Nutrition and Toxicology Research Institute Maastricht.

Intercellular adhesion molecule-1 (ICAM-1) expression is regulated by NF-κB activation and is involved in the recruitment of inflammatory cells to the side of inflammation. Inflammatory bowel disease (IBD) patients have increased intestinal ICAM expression. Fatty acids (FA) are known modulators of inflammation, because of their binding to PPARs, which can lower NF-κB activation. We therefore decided to evaluate effects of FA and PPAR agonists on ICAM expression. For this, differentiated caco-2 cells were stimulated with interleukine-1β plus interferon-γ to induce inflammation. After 16 hours, ICAM expression -measured by flow cytometry using a CD54 PE-labeled antibody- of stimulated cells was 2-fold higher as compared to non-stimulated cells. Two hours pre-incubation with troglitazon (PPARγ agonist) caused a 1.4-fold increase in ICAM expression, which was significantly lower than the 2-fold increase (P=0.017). Pre-incubation with Wy14643 (PPARα agonist) did not affect ICAM expression. Next, we evaluated effects of oleic acid (OA; C18:1,n-9), arachidonic acid (AA; C20:4,n-6) and eicosapentaenoic acid (EPA; C20:5,n-3). For this, cells were cultured with the FA for 3 weeks. ICAM expression of non-stimulated cells, cultured with AA was >1.5 times higher than that of cells cultured with OA and EPA. The increase in ICAM expression of cells cultured with AA and EPA was significantly lower as compared with OA (1.7 and 1.9-fold respectively; P<0.05). Consequently, ICAM expression after stimulation is highest with AA and lowest with EPA.
Conclusions: Our results indicate that PPARγ and not PPARα stimulation decreased ICAM expression. Particularly the n-6 PUFA AA was related to an increased ICAM expression, whereas the n-3 PUFA EPA decreased this expression. N-3 PUFAs might therefore be interesting mediators to inhibit intestinal inflammation in IBD patients. This effect may stem from a PPARγ-mediated reduction in NF-κB activation.

Cost study of high dose rate brachytherapy and stent placement in the palliation of dysphagia due to cancer of the esophagus and esophagogastric junction

S. Polinder, M.Y.V. Homs, P.D. Siersema, E.W. Steyerberg for the Dutch SIREC study group. Erasmus MC / University Medical Center Rotterdam.

Both high dose rate brachytherapy and metal stent placement are commonly used for palliation of dysphagia in patients with inoperable esophagogastric carcinoma. We aimed to study the potentially large costs of both treatments.
209 patients with dysphagia due to cancer of the esophagus and esophagogastric junction were randomized to high dose rate brachytherapy (12 Gy, n=101) or stent placement (Ultraflex stent, n=108). Costs were compared prospectively from a societal perspective, including comprehensive and detailed data. Detailed information on health care consumption was acquired from a standardized case record form and from monthly personal interviews by a specialized nurse.
The full cost price, based on real resource use, was much higher for stent placement (€1,500 vs. €570). Of patients randomized to brachytherapy, 54% also received a stent, while in the group of patients randomized to stent placement 22% received a second stent during follow-up. Patients randomized to brachytherapy were admitted on average 7.1 days longer in a health care institution than patients in the stent-group (23.4 vs. 16.3 days), caused by a longer period of stay in nursing homes for patients randomised for brachytherapy (11.0 versus 4.6 days). Intramural care was for both treatments by far the highest cost category (€7982 for brachytherapy and €6512 for stent placement ($p>0.50$)). Costs of medical procedures during follow up were significantly higher for stent placement (€249) than for brachytherapy (€168) ($p=0.005$). The costs of extramural care were €1278 and €1046 for brachytherapy and stent placement respectively. Total medical costs were similar for both treatments: €11,195 for brachytherapy vs €10,078 for stent placement ($p>0.50$).
There are only small differences between the total medical costs of brachytherapy compared to stent placement. Therefore, cost considerations should not play an important role in decision making on the appropriate palliative treatment strategy.

Limited transhiatal versus extended transthoracic resection for adenocarcinoma of the distal esophagus or cardia

J.B.F. Hulscher[1], J.W. van Sandick[1], A.G.E.M. de Boer[2], B.P.L. Wijnhoven[3], J.G.P. Tijssen[4], P. Fockens[5], P.F.M. Stalmeier[2], F.J.W. ten Kate[6], Van Dekken[7], H. Obertop[1], J.J.B. van Lanschot[1]. Depts of Surgery[1], Medical Psychology[2], Cardiology[4], Gastroenterology[5] and Pathology[6], Academisch Medisch Centrum Amsterdam, Depts of Surgery[3] and Pathology[7], Erasmus Medisch Centrum Rotterdam.

Controversy still exists about the optimal surgical approach for esophageal carcinoma.
Between April 1994 and February 2000, 220 patients with adenocarcinoma of the mid-/distal esophagus or gastric cardia involving the distal esophagus were randomized for transhiatal esophagectomy or transthoracic esophagectomy with extended en-bloc lymphadenectomy. Main end-points were overall survival and disease-free survival. Secondary endpoints were early morbidity and mortality, and cost-effectiveness.
106 patients were randomized for transhiatal esophagectomy, 114 for transthoracic esophagectomy. Demographic and tumor characteristics were comparable. Peri-operative morbidity was higher after transthoracic esophagectomy, leading to prolonged ventilation time, ICU/MCU-stay and hospital-stay. Hospital mortality was two percent and four percent resp.(p=0.45).
Radicality of surgery and pTNM stages were comparable. After a minimal potential follow-up of 2.5 years 142 patients had died, 74 (69%) after transhiatal resection and 68 (60%) after transthoracic resection. (p=0.12) Estimated five-year survival was 29% versus 39%; the estimated five-year survival benefit after extended transthoracic resection was 10% (95% C.I. –3% to 23%). This survival-benefit was 17% (95% C.I. –3% to 37%) for patients with a distal esophageal carcinoma, and only 1% for patients with a carcinoma of the cardia or gastro-esophageal junction. Costs of treatment were 23.809 euro after limited resection and 37.099 euro after extended resection.
Conclusion. Based on this “best available evidence” we consider transthoracic resection with extended en-bloc lymphadenectomy as the optimal resection-form for patients in good general condition with an adenocarcinoma of the distal esophagus, while we prefer transhiatal resection for tumors of the gastro-esophageal junction or gastric cardia.

The predictive value of alarm symptoms for upper gastrointestinal malignancies: results of a meta-analysis

G.A.J. Fransen[1], J.W.M. Muris[1], R.J.F. Laheij[2]. Dept of General Practice[1], University of Maastricht, Maastricht and Dept of Gastro-enterology[2], UMCN St. Radboud, Nijmegen.

With the advent of empirical treatment strategies, it becomes increasingly important to select patients with a high risk of having cancer for immediate endoscopy, without subjecting large numbers of patients without underlying malignant disease to unnecessary endoscopy, which is costly and troublesome to the patients. Usually alarm symptoms are used for this matter, but their predictive value is by no means clear, in spite of the amount of research conducted in this area.
The aim of this study was to investigate the predictive value of alarm symptoms indicating upper gastrointestinal malignancy, by means of a meta-analysis. Publications, identified through MEDLINE and manual search, had to fulfill the following criteria: endoscopic investigation of upper gastrointestinal malignancy, number of patients, prevalence of alarm symptoms, sensitivity, and positive predictive value (PPV) were described or could be calculated.
A total of 21 publications fulfilled the criteria, of which 12 case studies and 9 cohort studies. The prevalence of gastrointestinal malignancies of case studies and cohort studies was 100% and 2% respectively. For the case studies the weighted mean sensitivity for dysphagia, anemia/-bleeding, nausea/vomiting, and weight loss were respectively 47%, 28%, 21%, and 39%, for cohort studies 21%, 12%, 38% and 33%. The weighted mean PPV for these symptoms were respectively 5%, 2%, 4%, and 11%. Alarm symptoms were absent in 5% of the patients with a gastrointestinal malignancy.
In conclusion, the majority of patients with malignancies have alarm symptoms, however they are also often present in patients without malignancy. This results in relatively low sensitivity and PPV, and no apparent alarm symptom can be distinguished to indicate malignancy. More research is necessary to investigate the predictive value of combined presence of alarm symptoms in larger cohorts.

Effects of naturally occurring dietary anticarcinogens and non-steroidal anti-inflammatory drugs on rat hepatic and intestinal UDP-glucuronosyltransferases

E.M.J. van der Logt, H.M.J. Roelofs, E.M.M. van Lieshout, F.M. Nagengast and W.H.M. Peters. Dept of Gastroenterology, University Medical Centre St Radboud, Nijmegen.

Gastrointestinal tumours are among the most common malignancies in Western society. Several naturally occurring dietary compounds or nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce cancer rates. Earlier we showed that dietary administration of such agents enhanced the glutathione S-transferase enzyme activity in the rat gastrointestinal tract. Elevation of such phase II detoxification enzymes might be one of the mechanisms leading to cancer prevention. Now we investigated the effects of potential anticarcinogens (seven naturally occurring or synthetic compounds and six NSAIDs) on gastrointestinal UDP-glucuronosyltransferase (UGT) enzyme activities. Diets of male Wistar rats were supplemented with oltipraz, α-tocopherol, β-carotene, phenethylisothiocyanate (PEITC), sulforaphane analog compound-30, indole-3-carbinol, D-limonene, relafen, indomethacin, ibuprofen, piroxicam, acetyl salicylic acid or sulindac for two weeks. Hepatic and intestinal UGT enzyme activities were quantified by using 4-nitrophenol and 4-methylumbelliferone as substrates. Treatment with compound-30, D-limonene, or the NSAIDs indomethacin, ibuprofen and sulindac resulted in enhancement of proximal small intestinal UGT activities. Only compound-30 was able to induce mid- and distal small intestinal UGT activities. Large intestinal UGT enzyme activities were increased by ibuprofen and sulindac, whereas oltipraz, PEITC and D-limonene gave enhanced UGT enzyme activities in the liver. UGT enzyme activities were not influenced at all by α-tocopherol, β-carotene, indole-3-carbinol, relafen and acetyl salicylic acid. In conclusion, some dietary anticarcinogens or NSAIDs are capable of inducing UGT enzyme activities in the rat gastrointestinal tract. Effects were mainly seen in the proximal small intestine and liver. Enhanced UGT enzyme activities might lead to a more efficient detoxification of potentially carcinogenic compounds and thus could contribute to prevention of gastrointestinal cancer.

Oral calcium intake after first colonic polipectomy does not reduce polyp recurrence rate, a five years randomised clinical trial

E.T.P. Keulen, T.A.F. Engels, H.M.J.M. Verhoeven, L.P. Bos, L.G.J.B. Engels. Dept of Internal Medicine and Gastro-Enterology, Maasland Hospital Sittard-Geleen.

A previous study suggested that increased oral calcium intake might reduce colonic polyp recurrence rate.
Eighty-two subjects, diagnosed with one or more colonic tubular adenomas equal or greater than 1cm, were randomised to receive either 1000mg oral Calcium a day (CSF, n = 39) or no calcium substitution at all (con). Control colonoscopy was scheduled at 1 and 5 years after start of the trial. Subjects diagnosed with IBD, colorectal malignancy, polyposis coli or who required gut operations were excluded from the study. Also subjects diagnosed with urolithiasis, hypercalcaemia of renal failure were excluded. Analyses were performed on an intention to treat bases.
Five subjects did not complete the study: one died op pulmonary long embolism 3 months after start of the study (CSF), one subject was 1 year after initial tubular adenoma diagnosed with Crohn's Disease (CSF), one subject developed coecum carcinoma 4.5 years after initial tubular adenoma (con), requiring right hemicolectomy, one subject was diagnosed with pancreas carcinoma, one subjects refused to take calcium after 2 years (CSF). From 5 subjects (6%: 4 CSF, 1 controle) no follow-up data were available, despite routinely invitation for re-colonoscopy. Median follow-up was 59 months. In the CSF group 12 out of 35 (34.3%) developed new tubular adenoma's compared to 14 out of 42 (33.3%) control subjects. At all time points during the study now significant differences were observed. Overall 26 out of 77 subjects (33.8%) developed recurrent tubular adenomas.
In conclusion, in our randomised clinical trial with median follow-up of 5 years no difference in colonic polyp recurrence rate between calcium suppleted and a control group were observed. In total 33.8% developed recurrent polyps within 5 years of primary diagnosis, again underscoring the importants of frequent colonic surveillance in subjects diagnosed with tubular colonic adenomas.

Peripheral Blood Phenotyping in (Refractory) Coeliac Disease as a Marker of Pre-Malignancy?

M.S. Goerres[1], C.J.J. Mulder[2], P.J. Wahab[1], J.A.M. Kerckhaert[3], H. van Dijk[4]. Dept of Gastroenterology[1], Rijnstate Hospital, Arnhem and Dept of Gastroenterology[2], VU Medical Centre, Amsterdam and Immunology[3], Rijnstate Hospital, Arnhem and Immunology[4], Meander Medical Center, Amersfoort.

Coeliac disease (CD) is a T cell driven disorder mediated by gluten sensitivity, characterised by intra-epithelial T-cell lymphocytosis (IEL), crypthyperplasia and villous atrophy. A small subgroup of patients are known to develop (diet-) refractory CD (RCD). On the basis of IEL-phenotyping, RCD can be divided in type I with a normal intraepithelial T-cell phenotype and type II with aberrant intraepithelial T-cells, lacking surface expression of CD3. RCD type II is related to the development of Enteropathy Associated T- cell Lymphoma.
We hypothesised that this same aberrant T cell phenotype may also be present in peripheral blood samples, being safer, easier and cheaper to obtain than intestinal biopsies. In this pilot-study we evaluated peripheral blood T-cell phenotypes using flowcytometry, in patients with treated and untreated CD and RCD type I and II. Peripheral blood samples and intestinal biopsies of 5 untreated coeliacs, 8 treated coeliacs, 4 patients with RCD type I and 6 with RCD type II were obtained. Of all samples, T-cells were isolated and analysed using FACS.
In all untreated and treated coeliacs and in patients with RCD type I a normal intestinal and peripheral T-cell phenotype was seen, showing normal surface expression of CD3. In RCD type II, 3/6 patients had very small peripheral T-cell populations resembling the aberrant phenotype of intestinal T-cells. Two of 6 patients had a normal T-cell phenotype and another patient showed an aberrant, though non-characteristic, peripheral T-cell phenotype.
Conclusions: Untreated and treated coeliacs and patients with RCD type I all showed normal intestinal and peripheral T-cell phenotypes, as expected. In only 3/6 patients with RCD type II very low percentages of aberrant T-cells were present in peripheral blood samples. Therefore, the sensitivity of peripheral blood T-cell phenotyping to distinguish RCD type II from RCD type I and normal coeliacs is low in this pilot study.

Relationship between the CYP1A2–164A→C polymorphism (CYP1A2*1F) and risk for colorectal neoplasia in humans

H.J.J. Moonen[1], L.G.J.B. Engels[2], J.C.S. Kleinjans[1], T.M.C.M. de Kok[1]. Dept of Health Risk Analysis and Toxicology[1], Maastricht University and Dept of Gastroenterology[2], Maasland Hospital, Sittard.

Colorectal cancer (CRC) is one of the most common malignancies in Western countries, and is believed to be strongly related to dietary factors. More specifically, the intake of processed meat and of the formed heterocyclic aromatic amines (HCA) herein, is believed to play an important role in the etiology of CRC. HCA are metabolically activated by the enzymes cytochrome P4501A2 (CYP1A2) and N-acetyltransferase 2 (NAT-2). Respective genes encoding for these enzymes, show polymorphic distribution in the human population. These polymorphisms lead to variations in metabolic activities and may thus cause interindividual differences in cancer risk susceptibility. High activities for both CYP1A2 and NAT-2 are believed to be related to an elevated CRC risk. In the present study, we investigated the influence of genotypic and phenotypic variations for CYP1A2 and NAT-2 on the risk for colorectal neoplasia. The total study population comprised 94 individuals; 75 adenoma patients were assigned to different risk groups, based on the occurrence and size of the polyps, and compared with 19 endoscopically proven adenoma-free control subjects. All individuals were phenotyped for both CYP1A2 and NAT-2 using urinary caffeine metabolite ratios. Furthermore, subjects were genotyped for NAT-2 and the CYP1A2–164A-->C polymorphism (CYP1A2*1F) by means of PCR-RFLP.
Using logistic regression analysis, significant associations were found between the CYP1A2*1F polymorphism and the risk of colorectal neoplasia when comparing different risk groups or combinations of risk groups. For all other variables, no significant associations were found. These results indicate that the CYP1A2*1F polymorphism could play a role in colorectal cancer risk susceptibility in humans. Further study in larger populations is necessary to substantiate and extend these findings.

The yield of colonoscopy and sigmoidoscopy in a young population not at risk for familial colorectal cancer

A.E. de Jong[1,2], K.F. Wong[1], H. Morreau[3], H.F.A. Vasen[1,2] & The National Collaborative group on HNPCC and FAP. The Netherlands Foundation for the Detection of Hereditary Tumours[1], Leiden, Dept of Gastroenterology[2], Dept of Pathology[3], Leiden University Medical Center.

Information in literature on frequency of adenomas in young individuals (<50 yr) is scarce. We evaluated occurrence and characteristics of adenomas in a young population not genetically predisposed for the development of colorectal cancer (CRC).
The databases of the Dutch HNPCC/FAP Registry were used. The study population included relatives of HNPCC or FAP patients which had regular endoscopy until mutation analysis revealed they were not carrier of the (APC/MMR) gene defect identified in their family. We obtained results of surveillance examinations and pathology of all detected adenomas was revised.
We identified 247 (120M) HNPCC and 205 FAP (108M) relatives without a gene defect. In 338 subjects at least one colonoscopy (169M, mean age 38 yr) and in 98 subjects at least one sigmoidoscopy (55M, mean age 29yr) was performed. At first colonoscopy a total of 19 adenomas (9M, mean age 45yr) and 2 CRC (age 49 and 72yr) were identified, and at first sigmoidoscopy 2 adenomas (1M, age 8 and 40yr). In 23 subjects with, and in 162 subjects without an adenoma a follow-up colonoscopy was performed. Six of 23 subjects (26%) developed a new adenoma (all >50y) and 14 of 162 (9%) subjects developed their first adenoma during follow-up. In the colonoscopy group, the proportion of subjects free of adenomas at age 50 years was 85%, and in the sigmoidoscopy group 96%. Of all adenomas diagnosed during colonoscopy (n=45) 70% were located distal from the flexura lienalis. Of all adenomas (n=48), 14% were >7mm, 8% showed high-grade dysplasia and 5% showed villosity.
Although the frequency of adenomas in a young population not at risk for familial CRC is substantial, advanced pathology was rarely observed. On basis of our findings we conclude the risk of developing adenomas/CRC in young individuals without genetic risk factors is low. Surveillance programs should focus on young individuals with a positive family (or personal) history for adenomas or CRC, or on individuals >50 years.

Prevalence of ileal anal pouch adenomas in patients with familial adenomatous polyposis

P. Friederich[1], M. Berkhout[1], J.H.J.M. van Krieken[2], H.M. Vasen[3], F.M. Nagengast[1]. Dept of gastroenterology[1], UMCN, Nijmegen.

Familial adenomatous polyposis (FAP) is an autosomal dominant disease characterized by numerous adenomas in the colon. Most patients develop colorectal adenomas and consequently colorectal cancer. Proctocolectomy with ileal pouch anal anastomosis markedly reduces this risk. However, after this procedure adenomas and cancers have been described in the remaining rectal and ileal mucosa of the IPAA.
The aim of this study was to establish the prevalence of adenomas in the ileal pouch anal anastomosis (IPAA) of patients with familial adenomatous polyposis (FAP) in a referral University Centre and to determine whether chromo-endoscopy (CE) with indigo carmin enhances the diagnostic yield.
FAP patients with IPAA from our region of adherence were invited to have a detailed endoscopic examination of their pouch. The number of polyps was estimated before and after dye spraying. If present, minimally four biopsies were taken from polyps or normal appearing mucosa. Two pathologists examined all biopsy specimens. The biopsies were scored for inflammation, colonic metaplasia and dysplasia.
Thirty patients with a mean age of 32 years (18-76) and a male/female ratio of 17:13 were included. Adenomas were found in 21 patients (70%). The average length after the IPAA in patients with adenomas compared to patients without adenomas did not differ significantly (11,4 v.s.8.8 years; p=0.5). No differences between males and females were found. In 6 patients suspect polypoid lesions, all smaller than 5 mm, where identified only after CE. Although the study design was set up to evaluate the diagnostic properties of CE it seems to facilitate endo-scopic biopsies of suspected lesions. However the clinical relevance of these small adenomas is still unresolved.
In conclusion our study showed a marked prevalence of adenomas in the IPAA of 70%. The age of the IPAA was not significantly correlated with the occurrence of ileal pouch adenomas. Chromo-endoscopy can enhance the diagnostic yield.

Comparison of the glutathione S-transferase activity and isoenzym levels in the mucosa of the ileal pouchand afferent loop in familial adenomatous polyposis: possible risk factor for adenoma re-currence

P. Friederich[1], M. Berkhout[1], J.H.J.M. van Krieken[2], W.H.M. Peters[1], F.M. Nagengast[1]. Depts of Gastroenterology and Hepatology[1] and Pathology[2], University Medical Centre St. Radboud, Nijmegen.

Colectomy with ileal pouch anal anastomosis (IPAA) is the procedure of choice for treating patients with familial adenomatous polyposis (FAP). Howerver, after this procedure the risk for development of adenomas or adenocarcinomas in the ileal pouch remains. The pouch ileal mucosa adapts, due to the new luminal environment, with colonic metaplasia, which results in villous atrophy and crypt hyperplasia. Glutathione S-transferases (GSTs) have a protective role in carcinogenesis. Compared to the colonic mucosa GST activity in the normal ileum is higher, which may contribute to the fact that small intestinal carcinomas are scarce. Therefore colonic metaplasia could contribute to adenoma or carcinoma formation in the IPAA.
The aim of this study was to compare the glutathione related biotransformation system in the ileal pouch mucosa with the ileal mucosa of the afferent loop in FAP patients with an IPAA.
From 26 FAP patients who underwent IPAA, biopsies were taken from the pouch mucosa and the afferent loop up to 20 cm proximal of the pouch. The levels of GST classes alpha, pi, mu and theta were quantified by Western blotting, and the GST enzyme activities were measured by chloro-dinitrobenzene (CDNB) conjugation.
The results show a significantly lowered GST enzyme activity in the ileal pouch mucosa compared to ileal mucosa of the afferent loop (307 and 394 nmol/min/mg protein $p < 0,0001$, respectively). The GST alpha levels in the ileal pouch mucosa were also significantly lowered compared to the ileal mucosa of the afferent loop (respectively 4603 and 5285 ng / mg protein, $p < 0,01$). The GST pi and mu levels did not differ between the ileal pouch mucosa and the ileal mucosa of the afferent loop.
Conclusions: After IPAA the GST enzyme activity and the GST alpha levels are significantly decreased in the ileal pouch mucosa in patients with FAP, which may result in a deficient protection and enhance to the risk of adenomas or carcinomas in the ileal pouch.

Diagnostic accuracy of CT colonoscopy with intravenous contrast and without colonic cleansing versus conventional colonoscopy for the detection of colorectal polyps

J.M. Jansen[1], M.H.J. Voormolen[2], K.H. Schuur[2], W.N.H.M. Stuifbergen[1], A.W.M. Van Milligen de Wit[1]. Dept of Internal Medicine and Gastroenterology[1], Radiology[2], St. Elisabeth Hospital, Tilburg.

Colorectal cancer is the second leading cause of death related to cancer in the United States. More than 90% arise from adenomatous polyps. Screening for polyps reduces mortality and has proven to be cost-effective. A variety of screening tests are available. CT colonoscopy (CTC) is a relatively new technique to visualize the colon with similar diagnostic accuracy for polyps larger than 1 cm compared to conventional colonoscopy (CC). However it has several limitations.
To improve patient comfort and reduce procedure time we conducted a prospective study to evaluate the diagnostic accuracy of CTC with intravenous contrast and without colonic cleansing versus CC as the gold standard for the detection of colorectal polyps.
Twenty-five patients at high risk for colorectal neoplasia and polyps underwent CTC 1-2 weeks before CC. After administration of Buscopan® i.v. and pneumatic distension of the colon, contrast (Visipacque®) i.v. was administered and CT images were obtained in supine and prone position. Images were acquired using 5 mm collimation, 3 mm reconstruction interval, a table index of 7 mm at 120 kV and 100 mAs. 2D axial images were evaluated, additional 3D reconstructive images were created when necessary. The grade of patient discomfort was assessed by questionnaire. Endoscopists and radiologists were unaware of each others results.
CC showed no abnormalities in 10 patients. In 15 patients with one or more colorectal polyps present on endoscopy, CTC identified polyps (5mm – 3cm) in 5 patients. CTC resulted in one false-positive finding. Sensitivity, specificity and positive predictive value of CTC were 33%, 90% and 83%, respectively. The sensitivity of CTC appears unrelated to polyp-size. The patient discomfort data showed a high preference for CTC.
Conclusion: Although very well tolerated by our patients, CTC with intravenous contrast and without colonic cleansing showed inferior diagnostic accuracy compared to CC for the detection of colorectal polyps.

Malignant colorectal polyps: is endoscopic resection and follow-up a safe strategy?

F. ter Borg[1], A. Aslan[1], M. Ledeboer[1], J.W. Arends[2], M. Eeftinck Schattenkerk[3], E.H. Eddes[3]. Depts of gastroenterology[1], pathology[2] and surgery[3], Deventer Hospital.

Endoscopically removed colorectal polyps may contain carcinoma in situ (CIS) or invasive carcinoma (IC). Due to coagulation, it is often impossible to determine whether the endoscopic resection is radical (tumour continuous with coagulation area, TCCA), and surgical resection is advised when IC is present. We collected data on all CIS/IC polyps removed between 1995 and 2000. Thirty patients were encountered, eighteen men and 12 women. Mean age was 71 (48-90) years. There were 12 broad based adenoma's (BBA) (4 IC) and 18 stalked polyps (SP) (7 IC).
There were 12 radical endoscopic resections, including 2 BBA's (1 CIS, 1 IC) and 10 SP's (5 CIS, 5 IC). Median endoscopic follow-up (FU) in these patients was 27 (1-59) months with no tumour recurrence.
There were 18 endoscopic resections with TCCA. Seven underwent surgery Four out of seven were CIS polyps and showed T0-T1/N0 stages and could in retrospect have been managed endoscopically. Pathology of the colonic resections in 3 patients with an IC in a BBA showed 1x T1N1 and 2x T2N0 tumours. One of these 3 patients died 6 days postoperatively from pneumonia; the 2 other patients died during FU from metastatic disease.
The remaining 11 patients with TCCA were followed endoscopically. Five had BBA's (all CIS), six had SP's (3 CIS, 3 IC). All had FU endoscopy after 6-8 weeks, only 1 showed remnants of a BBA-CIS that was treated with coagulation. Unfortunately this patient refused FU. The others had a median endoscopic FU of 14,3 (2,4-45,8) months with no tumour recurrence. The 3 patients with a SP with IC+TCCA had FU of 4, 15, and 17 months without tumor relapse.
We conclude that additional surgical resection for BBA's harbouring IC with TCCA often reveals residual malignancy; our limited data suggest that BBA's with CIS and SP's with IC, even with TCCA, can be safely followed endoscopically, as is the case with BBA's and SP's polyps harbouring invasive carcinoma that have been removed completely.

Response to alpha-interferon prolongs survival and reduces the risk of hepatocellular carcinoma in chronic hepatitis B

M. van Zonneveld[1], H.G.M. Niesters[2], R.A. de Man[1], S.W. Schalm[1], H.L.A. Janssen[1]. Depts of Gastroenterology and Hepatology[1] and Virology[2], Erasmus Medical Center Rotterdam.

Data on the long-term effects of alpha-interferon (IFN) treatment on disease progression and mortality in patients with chronic hepatitis B(CHB) are limited. To evaluate factors influencing clinical outcome and survival, we performed a follow-up study on 165 HBeAg-positive CHB patients treated with IFN. Forty-eight patients received two or more courses of IFN. The median dose of IFN was 30 MU/week (range 2-70 MU/week), the median duration of therapy was 16 weeks (range 1-92 weeks). Eighty-seven patients (53%) were additionally treated with nucleoside analogues. Response to treatment was defined as HBeAg seroconversion within 12 months after the end of IFN therapy. Of the 165 patients 72% were male and 75% were Caucasian. Median follow-up was 8.8 years (range 0.3-24 years). Fifty-four patients (33%) responded to IFN treatment. Of the responders 52% lost HBsAg as compared to 9 % of the non-responders ($p<0.001$). Liver histology showed a decreased necroinflammatory activity and less progression of fibrosis in responders. Twenty-six patients died during follow-up, 16 of liver-related complications. Hepatocellular carcinoma was found in 8 patients, of which 6 were non-responders and one a responder who relapsed. The baseline factors age, albumin level and presence of liver cirrhosis were independent predictors of survival in multivariate analysis. Multivariate analysis showed a significantly improved survival (RR 0.25; 95% CI 0.09-0.70) and decreased risk of developing hepatocellular carcinoma in responders (RR 0.08; 95% CI 0.01-0.74). Responders also had a significantly improved survival if only cirrhosis was taken into account. We conclude that response to IFN therapy results in a prolonged virological remission with a increased rate of HBsAg seroconversion and improved liver histology. Response to IFN therapy increases survival and reduces the risk of developing hepatocellular carcinoma.

Hepatitis B virus genotypes in HBeAg-positive patients: geographic distribution and relation to viral replication and fibrosis

J.T. Sarneel[1], H.G.M. Niesters[2], R.A. de Man[1], S.W. Schalm[1], H.L.A. Janssen[1]. Dept of Gastroenterology and Hepatology[1], Dept of Virology[2], Erasmus Medical Centre, Rotterdam.

The aim of this study was to investigate the geographic distribution of HBV genotype and its relation to viral replication and histology in a predominantly Western population.
In a multicentre study we investigated 265 HBeAg+ CHB patients referred to liver units for antiviral therapy. All had detectable HBV-DNA (>103 gEq/ml) and transaminases above 2x ULN. None received antiviral therapy at time of bloodsampling. HBV genotype was assessed by sequence analysis. HBV-DNA was measured by taqman PCR. Biopsies were scored by Ishak-classification. Mean age was 35 years, 76% was male. The study population harboured 75% Caucasians, Asians 22%, Blacks <1% and mixed 3%. Patient geographic distribution was 38% from North-western Europe, 12% Eastern Europe, 32% Mediterranean, 11% East Asia and 6% North America.The prevalence of the HBV genotypes was A 33%, B 9%, C 14%, D 40%, E 1%, F <1%, G 1% and 2% both A and G. Caucasians were mainly infected by A (43%) or D (52%), Asians by B (40%) or C (58%). Genotype geographic distribution showed that in East Asia all patients were infected with genotype B (45%) or C (55%). In North America most patients were Asians and infected with B (29%) or C (59%). In the European areas genotype prevalence was: North-western Europe A 51%, B 7%, C 10% and D 24%, the Mediterranean area A 6%, B and C 0% and D 93% and Eastern Europe A 94% and D 6%. Mean log HBV-DNA was 9.05 for genotype A, B 8.52, C 8.57 and D 9.33. HBV-DNA level was significantly higher in D than in B and C ($p<0.003$). Mean ALT level as fraction of ULN was 4.2 for genotype A, B 4.3, C 3.7 and D 4.9 (p=NS). Fibrosis score was higher in genotype A than B, C and D ($p<0.042$, 0.007, 0.001 resp).
In conclusion, HBV genotype distribution in HBeAg+ CHB differs by ethnic origin and may reflect migration patterns. HBV genotype is associated with differences in virus replication and disease stage. Therefore HBV genotype should be assessed in epidemiological and therapeutic studies of CHB.

lytic and noncytolytic intrahepatic CD8 T-lymphocyte reactivity is important for response to antiviral therapy in chronic hepatitis B patients

T.J. Tang, J. Kwekkeboom, S. Mancham, R.S. Binda, J.G. Kusters, S.W. Schalm, H.L.A. Janssen. Dept of Gastroenterology and Hepatology, Erasmus MC, Rotterdam.

Strong intrahepatic CD8 T-cell and NK/NKT cell responses to HBV are associated with inhibition of viral replication. It is unclear whether noncytolytic mechanisms or direct cytotoxitity are involved in therapy-induced viral control. We investigated the intrahepatic CD8 T-cell and NK/NKT cell response in chronic HBV patients during antiviral therapy in relation to response (HBeAg seroconversion). Twenty chronic $HBeAg^+$ patients were treated with peg-IFNα (100μg sc/week) combined with lamivudine (100mg po/day) or placebo for 52 weeks. Intrahepatic immune cells were obtained by fine needle aspiration biopsy (FNAB). FNAB and peripheral blood were obtained at week 0, 2, 8 and 52. CD8 T-cell, NK/NKT cell, IFNγ (antiviral cytokine) and granzyme B (cytotoxic granules) were immunocytochemically stained. Positive cells were quantified per 1000 leucocytes in FNAB and blood. In all patients, the number of CD8 T-cells and NK/NKT cells were significantly higher intrahepatic compared to blood for all timepoints during therapy ($p<0.05$). During the first 8 weeks of therapy intrahepatic CD8 T-cells increased from 26 to 33 ($p=0.08$), but remained equal in blood ($p=0.22$). Responders (n=9) exhibited a significant increase in intrahepatic CD8 T-cells (week 0 vs. 8: 12.1 vs. 36.2, $p=0.008$), $CD8^+GrB^+$ T-cells (12.1 vs. 23.3, $p=0.008$) and $CD8^+IFN\gamma^+$ T-cells (1.2 vs. 3.4, $p=0.07$) during the first weeks of therapy; in nonresponders (n=11), no significant difference was found for any of these intrahepatic T-cells. In contrast to CD8 T-cells, a significant elevation of NK/NKT cells was observed at week 8 of therapy in nonresponders ($p=0.04$), but not in responders, suggesting conversion from an innate into an adaptive immune response in responders during therapy.
In conclusion, our results demonstrate that during antiviral therapy the intrahepatic CD8 T-cell response is important for control of HBV replication and that the antiviral effect is mediated by both cytolytic and noncytolytic mechanisms.

Recipient CTLA-4 +49 G/G genotype is associated with reduced incidence of acute rejection after liver transplantation

J. Kwekkeboom[1], Ph. de Reuver[2], V. Pravica[4], W. Hop[3], P. Boor[1], H.J. Metselaar[1], I.V. Hutchinson[4], H.W. Tilanus[2]. Depts of Gastroenterology and Hepatology[1], Surgery[2] and Epidemiology and Biostatistics[3], Erasmus Medical Center, Rotterdam, The Netherlands and Immunology Research Group[4], School of Biological Sciences, University of Manchester, UK.

An important factor in the activation of T-cells is the co-stimulation by CD80 and CD86 on Antigen-Presenting Cells. T-cells can express two ligands for these molecules: CD28, which is the stimulatory one, and CTLA-4, which is the inhibitory one. The aim of this study was to investigate whether acute rejection after liver transplantation is associated with single-nucleotide polymorphisms (SNP) in the CD86- and CTLA-4 genes of donors and recipients. SNP were determined in 135 recipients and in 73 donors. CD86 +1057 G/A genotype distributions in donors and in recipients were not associated with acute rejection. In univariate analysis recipient CTLA-4 –318 G/T and CTLA-4 +49 A/G genotype distributions were both weakly associated with acute rejection (p=0.07). Multivariate analysis revealed that the CTLA-4 +49 SNP, but not the -318 SNP, was independently of other risk factors, associated with acute rejection (p=0.04). Only 1 out of 13 CTLA-4 +49 G-homozygous recipients (8%) experienced acute rejection(s) compared with 40% of A/A or A/G recipients.The CTLA-4 +49 A/G SNP, which results in an amino acid substitution in the signal peptide of the protein, did, however, not affect intracellular expression or trafficking of CTLA-4 in T-cells, nor soluble serum CTLA-4 concentrations of the liver transplant recipients. In conclusion, this pilot study suggests that liver transplant recipients homozygous for CTLA-4 +49 G have a reduced risk of acute rejection.

Long term follow-up of interferon non-responders with chronic hepatitis C: Effect of glycyrrhizin on HCC development

B.E. Hansen[1,2], K. Ikeda[3], B.J. Veldt[2], E. Verheij[2], H. Suzuki[4], S.W. Schalm[2]. Dept of Epidemiology and Biostatistics[1], Erasmus Medical Center, Rotterdam, The Netherlands. Dept of Gastroenterology and Hepatology[2], Erasmus Medical Center, Rotterdam The Netherlands. Dept of Gastroenterology[3], Toranomon Hospital, Tokyo, Japan. Yamanashi Medical University[4], Yamanashi, Japan.

Glycyrrhizin (SNMC) is used as a treatment for patients with chronic hepatitis C in all academic units in Japan. However, the long-term consequences of SNMC therapy are not well documented. Aims: To study the occurrence of hepatocellular carcinoma (HCC) in interferon non-responder patients with chronic hepatitis C with or without subsequent SNMC therapy.
A meta-analysis was performed on individual patient data obtained from 12 Japanese university and major general hospitals. All consecutive chronic hepatitis C patients treated with interferon between 1 Jan 1990 and 31 Dec 1995 without sustained response were included.
Results: 1093 patients were included in the study. The mean follow-up was 6.1 years, SD 1.8, 461 patients received SNMC therapy. The overall HCC occurrence was 1.2%, 4.0%, 14% and 27% for fibrosis stage 1,2,3 and cirrhosis, respectively. In general, patients treated with SNMC suffered from more severe liver disease than those not treated with SNMC. To eliminate fibrosis stage as confounding factor, patients with fibrosis stage 3 or higher at inclusion (n=255) were selected.
Occurrence of HCC during follow-up was significantly reduced in patients treated with SNMC, according to multivariate Cox analysis with time-dependent covariates; hazard ratio 0.4; 95%CI [0.1; 1.0] p=0.04. This effect was more pronounced for patients showing response to SNMC treatment (ALT at week 16 < 1.5 x ULN); hazard ratio 0.3; 95%CI [0.1; 0.8] p=0.02.
Conclusion: SNMC therapy significantly reduces the risk for development of HCC in chronic hepatitis C patients with fibrosis stage 3 or higher, not responding to interferon-therapy.

Long term follow up of sustained responders to interferon alpha in chronic hepatitis C: A meta-analysis assessing true clinical endpoints

B.J. Veldt[1], G. Saracco[2], B.E. Hansen[3], S.W. Schalm[1], For the Eurohep* study group. Dept of Gastroenterology and Hepatology[1], Erasmus Medical Center, Rotterdam, The Netherlands, Dept of Gastroenterology[2], Ospedale Molinette, Torino, Italy, Dept of Epidemiology and Biostatistics[3], Erasmus Medical Center, Rotterdam, The Netherlands. *Eurohep study group participants are U. Hopf, Berlin; N. Boyer, Clichy; O. Weiland, Huddinge; F. Nevens, Leuven; I Castillo, Madrid; A.Bellobuono, Milan; C. Cammà and A. Craxi, Palermo; P. Marcellin, Paris; S.W.Schalm and J.T. Brouwer, Rotterdam and G.Saracco, Torino.

Sustained virological response at six months after treatment is the key outcome for treatment efficacy in hepatitis C. However, reports about the incidence of clinical events during long term follow up of European patients with a sustained response to interferon treatment are scarce.
Aims: To determine the virological relapse rate and to assess clinical endpoints during long term follow-up in European sustained responders to interferon treatment.
Methods: Meta-analysis of individual patient data of 8 European protocolled follow-up studies.
286 sustained responders were followed up for 59 months (range 12-120). Fifteen sustained responders had cirrhosis before treatment. HCV-RNA was detected in 25 (8.7%) of 286 sustained responders; the late relapse rate at five years of follow up was 10.5% (95%CI 6.5%-14.5%). The only factor predictive of late virological relapse was the total dose of interferon, acccording to multivariate analysis (Hazard Ratio=0.650; 95%CI 0.426-0.991, p=0.045); doses =< 216 MU being associated with the highest late relapse rate. Two patients originally not classified as having cirrhosis, developed decompensation at 30 and 60 months of follow up (rate of decompensation at 5 year follow up: 1.0% (95 %CI 0.0-2.3), the latter died of this decompensated cirrhosis. No HCCs were detected. The outcome in cirrhotic patients did not differ from other patients with sustained response to interferon.
Conclusions: The late virological relapse rate at five years of follow up was 10.5% (95%CI 6.5%-14.5%) in sustained responders to interferon treatment. Treatment with a high total dose of interferon reduces the risk of late virological relapse. The five year occurrence of clinical events was 1.0 % (95% CI 0.0-2.3) among 286 sustained responders.

Distinct intrahepatic immunological environment in chronic viral hepatitis analysed by flow cytometry of Fine-Needle-Aspiration-Biopsies

D. Sprengers, R.G. van der Molen, J. Kusters, J. Kwekkeboom, L.J.W. van der Laan, S.W. Schalm, H.L.A. Janssen. Dept Gastroenterology and Hepatology, Erasmus MC, Rotterdam.

In chronic hepatitis B and C virus infection it has been suggested that virus specific T cells are compartmentalised in the liver. Fine-Needle-Aspiration-Biopsy (FNAB) of the liver represents a safe and atraumatic method suitable for frequent cytological monitoring. We aimed to investigate whether flow cytometry of FNAB specimens allows accurate analysis of the intrahepatic compartment and whether the composition of liver infiltrating lymphocytes (LIL) differed from peripheral blood lymphocytes (PBL). In 17 consecutive patients with chronic viral hepatitis (8HBV,9HCV) we measured by flow cytometry the ratio CD8+ vs CD4+ lymphocytes, phenotype of CD8+ T cells, percentage CD56+ lymphocytes and interferon-γ production after stimulation with PMA/-ionomycin in peripheral blood mononuclear cells, in FNAB-cytology and in lymphocytes isolated from a tissue biopsy. The ratio CD8+ vs CD4+ lymphocytes in FNAB correlated with LIL from tissue biopsy (r=0.78) and differed from PBL (mean ratio CD8+/CD4+:2.7;2.3;0.7 resp.; $p<0.05$). Similar correlation was observed for CD56+ cells (r=0.91; mean %:14.7;16.7;1.7 resp.;$p<0.05$). The percentage IFN-γ producing lymphocytes in both FNAB and tissue biopsy was higher than in PBL (mean %: 40;45;22 resp.; $p<0.05$). Based upon CD45RO and CD27 expression LIL but not PBL contained predominantly CD8+ T cells of memory (CD45RO+ CD27+) and memory effector (CD45RO+ CD27-) phenotype and no difference in population with effector T cells was found. In conclusion, flow cytometry of FNAB-cytology provides an easy and accurate way to study the intrahepatic compartment. Compared to immunocytochemistry flow cytometry allows co-analysis of phenotype, functional status and specificity of subsets of immune cells. This enables efficient monitoring of intrahepatic immune events. Our data show a significant difference in populations and phenotype of immune cells present in the liver and peripheral blood of patients with chronic viral hepatitis.

Development of a novel, accurate and flexible limited sampling method for ciclosporin monitoring after liver transplantation avoids possible overdosing with trough level monitoring and underdosing with 2-hour monitoring

P. Langers, M.S.[1], S. Cremers, Ph.D.[2], J. den Hartigh, Ph.D.[2], R. Veenendaal, M.D.,Ph.D.[1], R. ten Hove, M.D.[1], J. Ringers, M.D.[3], C.B.H.W. Lamers, M.D., Ph.D.[1], B. van Hoek, M.D., Ph.D.[1]. Dept of Gastroenterology and Hepatology[1], Dept of Clinical Pharmacology[2] and Dept of Surgery[3], Leiden University Medical Center, Leiden.

Blood levels 2 hours after dosing (C-2) better than trough levels (C-0) reflect the 12-hour Area Under the Curve (AUC) for emulsified ciclosporin (CN) after liver transplantation (LT). We investigated difference in dosage, creatinin clearance (CRCL), blood pressure (BP), freedom from rejection and relation of C-2 and C-0 with AUC while switching 31 stable patients > 6 months after LT from C-0 to C-2 monitoring. Target-AUC was calculated based on C-0. The 62 AUC curves obtained were divided into 2 groups of 31 with similar AUC's. On one group 2-compartment limited sampling models (LSM) were calculated from dosing and measured blood concentrations using an iterative two-stage Bayesian procedure. As the golden standard the AUC of the other 31 curves was calculated using the trapezoidal rule. Prediction precision and bias were calculated. CN dose had to be reduced in 21/31 patients (68%) and remained unchanged in 10/31 (32%) after conversion from C-0 to C-2 monitoring. No increase in dose occurred. Mean lowering of dose was 69 mg daily (26,9% of initial dose, $p<0.0001$). Mean increase of CRCL was 7,93 ml/min (11,6% of initial CRCL, $p=0.016$). Only systolic morning and mean morning BP decreased slightly but significantly. Diastolic morning BP and afternoon BP did not change. Mean C-2 values were 666 ± 23 ug/l. C-2 correlated better ($r^2=0,75$) than C-0 ($r^2=0.64$) with AUC, but there were variable C-2 levels with the same dose. On C-2 monitoring 13/21 patients had an AUC below the target, 2/13 developed rejection. LSM 0+1+2h ($r^2=0,92$), 0+1+3h ($r^2=0,95$) or 0+1+2+3h ($r^2=0,96$) have much better correlation with AUC, no fixed time points are needed, avoiding the dangers of overdosing with C-0 and underdosing with C-2 monitoring.

Follow up of Epstein Barr virus polymerase chain reaction after liver transplantation in pediatric patients

R. Scheenstra[1], E.A.M. Verschuren[2], S.J.C. Stevens[3], T.H. The[2], H.J. Verkade[1], C.M.A. Bijleveld[1]. Dept of Pediatric Gastroenterology[1] and Clinical Immunology[2], Academical Hospital Groningen, Dept of Pathology[3], Free University, Amsterdam.

Post Transplantation Lymphoproliferative Disease (PTLD) is one of the major causes of morbidity and mortality in transplantation patients. A primary Epstein Barr infection is one of the major risk factors for developing a PTLD. The increased risk might be related to a higher circulating viral load.
The aim of this study was to determine circulating EBV load the first half year after transplantation in relation to primary EBV infection. All children who received a liver transplant in 2000 or 2001 in Groningen were included. EBV serology was performed before transplantation. At regular intervals a competitive quantitative PCR for EBV Nuclear antigen-1 was performed. Patients were followed for development of a PTLD.
13 patients were included. 4 patients were EBV seropositive before transplantation and 9 patients were EBV seronegative before transplantation. Of the 4 patients who were EBV seropositive before transplantation, in only one patient 2 positive EBV DNA values above the cut-off point of 2000 copies/ml were found, with a peak viral load of 3600 copies/ml. None of these patients developed a PTLD. In the 9 patients who were EBV seronegative before transplantation 8 patients did pass an EBV infection after transplantation. Positive EBV DNA samples were seen in these patients at least three measurements. The first detectable viral load was at a mean of 64 days after transplantation (range 38-89). The mean peak viral load was 79,7000 copies/ml (3,600 –446,000). Two of these patients developed a PTLD. Conclusions: In the patients with a primary infection after transplantation we found more EBV DNA positive samples and a higher EBV viral load than in the patients who were EBV seropositive before transplantation. These results are compatible with the concept that the increased risk on PTLD in pediatric liver transplantation during a primary EBV infection is related to high circulating viral loads.

Prevalence of other diseases in patients with primary biliary cirrhosis (PBC)

P.C.J. ter Borg[1], H.R. van Buuren[1], C.M.J. van Nieuwkerk[2], E.B. Haagsma[3], J.W. den Ouden[4], M.H.M.G. Houben[5], R.W. de Koning[6], E.W. van der Hoek[7], R. Adang[8], G.P. van Berge Henegouwen[9] for the Dutch Multicenter PBC study group. Dept of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam[1], Dept of Gastroenterology and Hepatology, VU Hospital, Amsterdam[2], Dept of Internal Medicine, University Hospital, Groningen[3], Dept of Internal Medicine, St. Franciscus Hospital, Rotterdam[4], Dept of Internal Medicine, Rode Kruis Hospital, Den Haag[5], Dept of Internal Medicine, Canisius Hospital, Nijmegen[6], Dept of Internal Medicine, Carolus Hospital, Den Bosch[7], Dept of Internal Medicine, VieCuri MC, Venlo[8], Dept of Gastroenterology and Hepatology, University Medical Center, Utrecht[9].

PBC is a presumed autoimmune chronic liver disease. Several reports emphasized the prevalence of associated disorders in PBC. An association with the following disorders has been quantified in previous studies: thyroid dysfunctions and rheumatic disorders seem common. Additional associations have been described with SLE, systemic sclerosis, renal tubular acidosis, bacteriuria, celiac disease, ulcerative colitis and malignant diseases.
Since most of these studies seemed to be initiated because of a suspected association, significant bias may have occurred.
In order to minimize the occurrence of selection we undertook the present study to quantify the prevalence of all previously reported associated diseases as well as other disorders in a large, prospectively followed cohort of 237 PBC-patients. No specific screening studies were performed for diagnosing clinically occult disorders.
Mean follow-up was 11 years. No association with celiac disease was found. There was a high prevalence of rheumatic diseases and Raynaud syndrome (total 14%) and endocrine disorders (16%): diabetes (9%), thyroid disorders (7%). The prevalence of GE-diseases was similar to the general population (gallstones 20%, peptic ulcers 6%, reflux oesophagitis 4%). There was no clear-cut association with malignnant diseases (breast cancer 4%, colorectal cancer 2%, skin cancer 2%), with the exception of hepatocellular carcinoma (2%).

Conclusions: There seem only few truly associated diseases with PBC. These are rheumatoid disorders (rheumatoid arthritis and Raynaud syndrome) and thyroid disorders (thyroiditis and hypothyroidism). We could not confirm the association with celiac disease or with malignant disease with the exception of hepatocellular carcinoma. Associated disorders in an unselected population of PBC-patients are only limited to a very few specific diseases. Most co-existing diseases have comparable frequency with the general population.

Increased mucosal expression of Matrix MetalloProteinases-2 and –9 in inflammatory bowel disease and the prognostic impact for relapse in Crohn's disease

M.J.W. Meijer[1], W. van Duijn[1], M.A.C. Mieremet-Ooms[1], J.M. van der Zon[1], G Kuiper[1], R.A. van Hogezand[1], R. Hanemaaijer[2], J.H. Verheijen[2], C.B.H.W. Lamers[1], H.W. Verspaget[1]. Dept of Gastroenterology-Hepatology, Leiden University Medical Center, Leiden[1], Gaubius Laboratory, TNO-PG, Leiden[2].

Enhanced intestinal expression of basement membrane degrading Matrix MetalloProteinases (MMP)-2 and -9 may accelerate tissue damage in Crohn's disease (CD) and ulcerative colitis (UC). Therefore, these enzymes could also be involved in the development of recurrence after surgical resection. First operation mucosal tissue resections (n=111) from CD patients, with a minimal 5 year follow-up, were homogenised in 0.1 M Tris pH 7.5, 0.1% (w/v) Tween 80, next to resection tissue from mostly pancolitic UC patients and colorectal cancer controls (respectively, n=35 and 66). Total protein, MMP-2 and MMP-9 were measured using the method described by Lowry and specific ELISAs, respectively. Group differences were assessed using Kruskal-Wallis, Mann-Whitney U, Wilcoxon signed ranks tests and association with diagnostic and surgical recurrence using the log rank test. Median levels of MMP-2 and MMP-9 were similar in macroscopically inflamed colonic CD and UC tissue and significantly higher ($P<0.01$) compared to paired non-inflamed tissue or location matched controls. In inflamed CD ileum, MMP-2 and MMP-9 were also higher compared to paired non-inflamed CD (resp. $P<0.01$ and $P=0.07$) and controls (resp. $P=0.2$ and $P<0.001$). In relation to recurrence, we found that a MMP-2 level higher than 95 ng/mg protein in inflamed CD colon was associated with a shorter interval to second operation, i.e., 8.9 vs. 13.4 years ($P=0.05$). A level of MMP-9 higher than 55 ng/mg was associated with a shorter time interval to clinical/endoscopical relapse, i.e., 4.7 vs. 10.5 years ($P=0.07$). In inflamed ileum, no prognostic value of MMP could be discerned. These results show the potential involvement of MMP-2 and MMP-9 in IBD pathogenesis. In addition, their measurement in inflamed colonic CD mucosa seems to identify patients prone to relapse.

A functional single nucleotide polymorphism of the TLR4 gene is correlated with Crohn's disease and not with ulcerative colitis

H. Braat[1], M. Dijkgraaf[2], W. Curvers[1], E. Vogels[1], A. van Bodegraven[3], P. Stokkers[4], D. Hommes[4], S. van Deventer[4]. Dept of Experimental Internal Medicine[1] and Dept of Biostatistics[2] and Dept Gastro-intestinal Disease VUMC[3], and Dept of Gastro-intestinal Disease AMC[4], Academic Medical Center, Amsterdam.

A subpopulation of patients with Crohn's Disease (CD) suffers from a mutation in the Nod2 Pattern Recognition Receptor (PRR). Several groups of PRR have been described including the Toll Like Receptor (TLR) family that consists of ten different subtypes. One of the members of the TLR family is TLR4, a PRR for Lipopolysacharides (LPS) of Gram negative micro-organisms able to activate NF-κB. Three different Single Nucleotide Polymorphisms (SNP) have been described for the *Tlr4* gene. The A299G missense mutation is responsible for airway hypo-responsiveness in humans after LPS inhalation. To determine the prevalence of the SNP A299G of the *Tlr4* gene in patients with inflammatory bowel disease. Genomic DNA from 356 patients with CD, 244 patients with Ulcerative Colitis (UC) and 164 controls was screened for the SNP Ala299Gly of the *Tlr4* gene. The screening was accomplished by a polymerase chain reaction -restriction fragment- length polymorphism assay and the primers were chosen to create restriction sites in the mutant alleles. Binary logistic regression analysis was performed to estimate the influence of the *Tlr4* SNP on the presence of CD and UC respectively, a positive influence of the *Tlr4* SNP on CD was hypothesized. 7 patients (2 with UC and 5 with CD) were homozygous and ninety individuals were heterozygous (19 controls, 29 with UC and 47 with CD) for the *Tlr4* SNP (Table 1). The odds ratio for the TLR4 coefficient equals 1.83 for CD(with a lower 95% confidence limit of 1.09) and 1.56 for UC (with a 95% confidence interval of 0.80-3.03). The presence of the SNP A299G of *Tlr4* increases the risk of suffering from CD. Here, we describe a correlation of a functional SNP of the *Tlr4* gene with CD but not with UC. Both, mutations in Nod2 and TLR4 predispose to the development of CD but not to the development of UC.

Reciprocal regulation of HO-1 and iNOS in intestinal epithelial cells in response to oxidative stress

G. Dijkstra, H. Blokzijl, L. Bok, M. Homan, P.L.M. Jansen, M. Moshage.
Dept of Gastroenterology and Hepatology, University Hospital Groningen.

Background: Inducible Nitric Oxide Synthase (iNOS) is expressed in intestinal epithelial cells (IEC) of patients with active inflammatory bowel disease and in epithelial cells of endotoxemic rats. The induction of iNOS in IEC is a NF-kB mediated survival pathway of IEC.The transcription factor AP-1 is induced by oxidative stress and one of its target genes is heme oxygenase 1 (HO-1). The enzyme HO-1 produces carbon monoxide (CO) which may attenuate the inflammatory response.
Aim:To determine the effects of oxidative stress on iNOS and HO-1 induction in IEC.Methods:In endotoxemic rats (in vivo model) the thiol-modifying agent diethylmaleate (DEM) and in human coloncarcinoma cells DLD-1 (in vitro model) both DEM and the lipid peroxidation end product 4-hydroxynonenal (4-HNE) were used to induce oxidative stress. Rats were treated with DEM 0.5 hr before and 3 hrs after LPS injection (5mg/kg ip). Rats were sacrificed 6 hr after LPS administration. DLD-1 human colon carcinoma cells were exposed to a cytokine mix (CM) for 8 hr. DEM or 4-HNE were added 0.5 hr prior to and 4 hr after addition of CM. HO-1 and iNOS expression was evaluated by RT-PCR , Western blot and immunohistology.
Results: In vivo: LPS strongly induced iNOS in IEC of the ileum and colon but did not induce HO-1. Combined treatment with LPS and DEM abolished iNOS expression but strongly induced HO-1 expression. In vitro: Cytokines induced iNOS expression but did not induce HO-1 expression in DLD-1 cells.DEM and 4-HNE treatment prevented iNOS induction but increased the HO-1 expression in CM-exposed DLD-1 cells.
Conclusion: In the presence of oxidative stress NF-kB mediated iNOS expression is switched off and AP-1 mediated HO-1 expression is switched on in IEC. These findings indicate that in IEC, NF-kB regulated defense mechanisms are important when the anti-oxidant status is still intact, whereas AP-1 regulated.defense mechanisms are important when the anti-oxidant status is poor.

Inhibition of cyclooxygenase activity reduces rotavirus infection*

J.W.A. Rossen, J. Bouma, H.C. Raatgeep, H.A. Büller and A.W.C. Einerhand. Lab of Pediatrics, Erasmus MC - Sophia Rotterdam.

Rotavirus (RV) diarrheal illness is a common infectious disease in young children. RVs infect mature enterocytes in the small intestine leading to induction of virus gene expression and inflammatory cytokines, reduction of enterocyte gene expression and vacuolization. Cyclooxygenases, COX1 and COX2, are enzymes that synthesize prostaglandins (PGs). Two observations point toward a role of COXs in RV infection: 1. The duration of RV diarrheal illness is reduced after oral aspirin, a non-specific COX inhibitor. 2. Elevated levels of PGs have been recorded in the plasma and stool of RV-infected children. To study the role of COXs and PGs in RV infection, human intestinal Caco-2 cells, susceptible to RV infection, were incubated with COX1-specific, COX2-specific or non-specific (Indomethacin) COX-inhibitors prior to and during inoculation with 100 focus forming units of the human RV Wa strain. The number of infected cells was monitored by an indirect immunofluorescence assay using an anti-RV polyclonal antiserum. Similar experiments were performed using inhibitors of MEK (activating the ERK1/2 and ERK5 pathway), PKA (activating the ERK1/2 pathway) and p38 MAPK, all involved in regulation of COX2 gene expression. In addition, PGE2 levels were determined at different time-points postinfection (p.i.) using a PGE2 enzyme immunoassay system and the kinetics of the infection was monitored by Western blot analysis. In infected Caco-2 cells viral replication was detectable from 4 h p.i. This coincided with an increase in PGE2 levels. Indomethacin and specific COX-inhibitors reduced the RV infection by 75% and 50%, respectively. Moreover, Indomethacin reduced virus infection when added after virus binding. Also the inhibitors of MEK, PKA and p38 MAPK were able to block RV infection by at least 40%. The effect of the COX-inhibitors and the inhibitor of PKA but not that of MEK could be counteracted by adding PGE2. In conclusion, COXs and PGE2 are important mediators of RV infection.

Celecoxib directly interferes with the Wnt pathway independent of Cox-2 in colon cancer

J.B.Tuynman, R.van der Neut, M.P. Peppelenbosch, D.J. Richel.
Academisch Medisch Centrum, Amsterdam.

NSAIDs and selective cyclooxygenase-2 (Cox-2) inhibitors possess anti-carcinogenic potential against adeno-carcinoma's including colo-rectal carcinoma (CRC). The mechanism underlying these effects are subject to intense debate but may be partially explained due to inhibition of tumour cell Cox-2. The chemopreventive effects, however, suggest the involvement of other mechanisms in an early phase of carcino-genesis, since Cox-2 expression occurs late in the carcinogenesis. The main event in early CRC carcinogenesis is the APC mutation resulting in the formation of Beta-catenin/TCF complex. Subsequently, the oncogenes C-Myc and C-Met are expressed. We hypothesized that the anti-carcinogenic effects of selective Cox-2 inhibition in CRC occurs in this early phase of the carcinogenesis. The effects of celecoxib on the transcription and expression of Wnt targets was evaluated in colon cancer cell lines. To evaluate protein levels, western blot analysis was performed. RNA levels were determined with a quantitative RT-PCR. To determine the level of Beta-catenin/ TCF dependent transcription of Wnt related oncogenes we performed a luciferase reporter assay.
Celecoxib administration resulted in a concentration dependent de-crease of viability and an increase of activated caspase 3 levels in three cell lines, independent of COX-2 expression. Protein and RNA levels of the Wnt targets C-Met and C-Myc were down regulated in the presence of celecoxib at serum levels. In addition the beta catenin/TCF mediated transcription was down regulated. We show that the anti-carcinogenic effects of celecoxib involve inhibition of Wnt signalling resulting in down regulation of the oncogenes C-Myc and C-Met. This is a Cox-2 inde-pendent mechanism. Since the importance of the Wnt pathway in early carcinogenesis is widely recognised our results strongly suggest that Celecoxib has a significant chemopreventive and therapeutic potential.

Mesalazine acts directly on the Wnt/APC/beta-catenin pathway via protein phosphatase 2A

C.L. Bos[1,2], M.P. Peppelenbosch[2], J.C.H. Hardwick[3], D.J. Richel[1]. Dept. of Medical Oncology[1] and Experimental Internal Medicine[2] and Gastro-enterology[3], Academic Medical Center, Amsterdam.

Apart from anti-inflammatory features, mesalazine usage in Colitis Ulcerosa is associated with a reduced incidence of colorectal cancer. As in contrast to other non-steroidal anti-inflammatory drugs mesalazine displays few side effects during long-time treatment, mesalazine may form an interesting component of chemopreventive strategies with respect to colorectal cancer. Rational usage of mesalazine in this respect is, however, hampered by a lack of understanding with respect to the underlying molecular mechanisms mediating this chemopreventive effect. We therefore investigated the effect of mesalazine on two colon cancer cell lines, DLD-1 and SW480, and aimed our studies at the most important pathway in colon cancer, the Wnt/APC/beta-catenin pathway. We observed that mesalazine dose- and time-dependently reduced the activity on the Wnt/beta-catenin pathway, as assayed by the TOP-FOP reporter assay. This effect was confirmed at the protein level by looking at the phosphorylation status of various elements of the Wnt/beta-catenin pathway by Western blot analysis. Importantly, mesalazine treatment caused increased phosphorylation of protein phosphatase 2A (PP2A), an event associated with inhibition of PP2A enzymatic activity. This effect on the phosphorylation of PP2A is functional, as mesalazine treatment of cells decreases enzymatic activity of PP2A. Since PP2A is a well-established positive regulator of the Wnt/APC/beta-catenin signalling cascade, these findings suggest that chemopreventive effect of mesalazine is mediated via inhibition of PP2A enzymatic activity followed by subsequent down regulation of the Wnt/APC/beta-catenin pathway via influencing PP2A as a possible molecular mechanism underlying the chemopreventive effect of mesalazine.

Dynamic MRI of Gastric Motility and Emptying: Response to Somatostatin in Healthy Subjects

I.M. de Zwart, A.de Roos, H.J.Lamb, P.Kunz, A.A.M. Masclee, Leiden University, Medical Center, Dept. of Radiology and Gastroenterology.

The effect of somatostatin on gastric emptying and motility is not well understood. Whereas some studies suggest that somatostatin enhances gastric emptying and motility, other studies show the opposite effect. A shortcoming is that motility and emptying have not been measured simultaneously. MRI allows the evaluation of both emptying and motility simultaneously.
Dynamic MRI was performed in eleven healthy subjects (5F, 6M; age range 18-50yrs) in two sessions during continuous intravenous infusion of saline or somatostatin (250mcg/h) in random order. Gastric motility (i.e. the number of peristaltic contractions and the contraction pattern) and gastric emptying were evaluated using 3D-volume scans and 2D-dynamic scans. Measurements were obtained before and at regular intervals after a single ingestion of a 600kCal meal of 400ml mixed with gadolinium during 90min. Measurements during saline infusion were compared to measurements during somatostatin infusion to assess potential changes in gastric physiology.
Total gastric volume did not differ significantly between both experiments before and directly after meal ingestion. During somatostatin, total intragastric volume after 90 min was significantly lower than during saline infusion (287.5±31.4ml vs 403.6±18.8ml, $p<0.05$). Meal volume was significantly lower during somatostatin infusion up to 45 minutes after meal ingestion (at 45 min : 262±23.5ml vs 374±33.7ml during saline infusion, $p<0.05$), but did not differ significantly thereafter. After meal ingestion, the contraction pattern became irregular during saline infusion. During somatostatin, the contraction pattern remained regular. The number of contractions did not differ between the saline and the somatostatin session (14.4±0.3 vs 14.6±0.4 contractions per 5 min, $p>0.5$).
Conclusion: Somatostatin enhances initial gastric emptying and reduces total postprandial gastric volume pointing to impaired relaxation of the stomach.

A comparison of azathioprine-induced pancreatitis in Crohn's disease versus other diseases

R.K. Weersma[1], F.T.M. Peters[2], L.E. Oostenbrug[2], A.P. Van den Berg[2], R.J.Ploeg[3], M. Van Haastert[4], H.M. van Dullemen[1]. Dept of Gastro-enterology and Hepatology[1], Medisch Spectrum Twente, Enschede, Dept of Gastroenterology and Hepatology[2] and Dept of Surgery[3], University Hospital, Groningen, Dept of Gastroenterology and Hepatology[4], Martini Hospital, Groningen.

Azathioprine is widely used in Crohn's Disease (CD). A major drawback is the occurrence of side effects, especially acute pancreatitis (AP). Review of the literature shows that AP is rarely seen when azathioprine is used for other diseases than CD.We conducted this study to investigate wether AP occurs especially in patients with CD and if there is a variation in side effects for different diseases.
The study is a retrospective analysis of patients using azathioprine after liver or renal transplantation (LT/RT), for systemic lupus erythemathosis (SLE), Wegener's granulomatosis (WG), autoimmune hepatitis (AIH), rheumatoid arthritis (RA), ulcerative colitis (UC) or Crohn's disease (CD). A computerized search using the term "azathioprine" or "Imuran" was done on the Hospital Information System of the University Hospital Groningen, resulting in 1563 Patients matching our criteria. 67 patients with CD or UC from a community hospital were added.
Azathioprine-toxicity necessitating withdrawal occurred significantly ($p<0,05$) more in RA (78/317), UC (24/120) and CD (60/264) compared to SLE (5/73), WG (6/85), AIH (8/129), LT (17/254) and RT (22/388). 12/264 patients with CD had AP (4,5%) compared to 2/129 with AIH, 1/120 with UC, 2/388 after RT, 1/254 after LT. AP did not occur in patients treated for SLE, WG or RA. AP was more prevalent in CD than in any other disease. Of all patients, who experienced AP, 14 were female and 4 male.
Conclusion: Azathioprine-induced toxicity and the necessity of with-drawal is more common in UC, CD and RA than in other diseases. Acute pancreatitis due to azathioprine is strongly associated with CD and rarely occurs with other underlying conditions. Females have a higher risk than males to develop azathioprine-induced AP. An idio-syncratic drug reaction in combination with a genetic predisposition is supposed.

Maintenance treatment with Budesonide 6mg versus 9mg once daily in patients with Crohn's disease in remission

D.J. de Jong[1], D.J. Bac[2], T.G. Tan[3], S.Y. de Boer[4], J.B.M.J. Jansen[1], T. Hoofwijk[5], R. Müller[6], A.H.J. Naber[1]. Dept of Gastroenterology[1], University Medical Centre Nijmegen, Ikazia Hospital Rotterdam[2], Hospital Midden Twente Hengelo[3], Slingeland Hospital Doetinchem[4], Tramedico International BV Weesp[5], The Netherlands, Dr. Falk Pharma GmbH Freiburg[6], Germany.

In previous controlled trials, budesonide 6mg once daily was able to prolong the time to relapse in patients with Crohn's disease (CD)in clinical remission. However, the rate of relapses after one year (59 to 61%) was not statistically different from placebo treated patients (63 to 67%). Furthermore, budesonide 9mg/d was effective in active CD with limited side effects. The aim of the present study was to determine if budesonide 9 mg/d maintenance therapy was more effective than 6 mg/d without an increase in adverse events (AE's).
Methods: Double blind randomised trial in patients with CD in remission (CDAI below 150 points). Patients were randomised between 6 mg/d or 9 mg/day of budesonide (Budenofalk capsule 3mg). All other medical treatment for CD was discontinued. Primary end points of the intension to treat analysis were the time to relapse and relapse rates after one year of treatment. Relapse was defined by a CDAI above 150 points with an increase of at least 60 points.
Results: Of 157 patients, 76 were randomised to 6 mg/d and 81 patients to 9 mg/d. After one year, relapse rates were 22.4% in the 6 mg/d group and 18.5% in the 9 mg/d group. Furthermore, in these groups, 14% and 17% of patients discontinued therapy without relapse. These differences are not significant. Survival analysis showed no differences in the time to relapse. AE's were reported in 61% of patients with 6 mg/d treatment and 66% with 9 mg/d treatment, but only the minority was probably drug related. All 12 serious AE's were unrelated or unlikely drug related (4 in 6 mg/d group and 8 in 9 mg/d group).
Conclusion: In quiescent CD, no additional benefit was demonstrated by increasing the dose of budesonide to 9 mg once daily to maintain remission. However, this may be caused by the low relapse rate that was already achieved in the control group, treated with 6 mg/d of budesonide. Therefore, 6 mg/d of budesonide seems a reasonable dose for maintenance therapy in Crohn's disease.

Intravenous Pamidronate in Combination with Calcium and Vitamin D Is Highly Effective for Treatment of Low Bone Mineral Density in Crohn's Disease

P. Stokkers[1], T. Schreuder[2], M. Deley[1], M. van der Spek[1], S. van Deventer[1], C. Mulder[2], D. Hommes[1]. Academisch Medisch Centrum[1], Amsterdam, Rijnstate Ziekenhuis[2], Arnhem.

Decreased bone mineral density is common in Crohn's disease (CD), and may be underestimated and under diagnosed. The prevalence of osteoporotic fractures in CD is 22 percent. Orally available biphosphonates have been associated with gastrointestinal side effects, and the absorption is only 1-2 percent. We investigated whether intravenous pamidronate is a safe and effective treatment.
Twenty-nine CD patients with decreased bone mineral density (BMD) as assessed by DEXA-scan were treated with calcium 1000mg and vitamine D 400IU daily. In addition 30 mg of pamidronate was administered intravenously every 3 months. Osteopenia was defined as a score between minus 1 and minus 2.5, osteoporosis was defined as a score below minus 2.5. DEXA-scanning was performed before initiating treatment, after 6 months and after 1 year. Treatment efficacy was evaluated by performing a paired T-test using the SPSS 11.5 software program.
Of 29 CD patients 21 patients were osteoporotic and 8 were osteopenic. Twenty patients were female, with a mean age of 43, 9 patients were male, with a mean age of 40. In one patient treatment was discontinued because of fever after infusion. Otherwise tolerability was excellent and no adverse events were documented. A mean of 4.2 (SD1.4) pamidronate infusions were administered during 12.7 (SD4.2) months. A mean increase of lumbar spine T-scores was observed of 4.3%(SD 3.5) The effect of treatment on femoral T-scores was less pronounced: 2.4% (SD3.5).
We conclude that intravenous pamidronate in combination with calcium and vitamin D is a well tolerated strategy to treat CD associated osteopenia and osteoporosis. Although uncontrolled, treatment results in a significant increase of bone mineral density in the lumbar spine, which could reduce the reported increase of fractures in these patients. A longer treatment period is probably needed to appreciate bone mineral density changes in the femoral neck.

Probiotics (VSL#3) in Arthralgia. Preliminary results of an ongoing open trial in patients with ulcerative colitis and Crohn's disease

O. Karimi, A.S. Peña, A.A. van Bodegraven. Dept of Gastroenterology and Lab of Immunogenetics, VUmc, Amsterdam.

Background: Arthralgia is a common extraintestinal manifestation of IBD with prevalence between 10% and 25%. NSAID are often efficacious, but may induce a flare-up of IBD. Aim: We are determining the safety and efficacy of open label VSL#3 (sachets containing 900 billion viable lyophilized bacteria of 4 strains of Lactobacillus, 3 strains of Bifidobacterium, and one strain of Streptococcus salivarius subsp. thermophilus in arthralgia in patients with quiescent IBD. Methods: 17 patients (18 to 70 years) with quiescent IBD were given 2 sachets VSL#3 per day for 3 months. Inclusion required complaints of arthralgia for more than 2 weeks with stable medical therapy. Arthralgia was assessed by the Ritchie score (joints assessed separately and graded for tenderness on a 0-3 scale) and the visual analogue scale, applied to the week before assessment (VAS I) and at the day of examination (VAS II). At week 6, assessments of complaints were conducted by a telephone interview and the patients were asked to complete both VAS. At 12 weeks, the Ritchie and VAS score was reassessed in the Outpatient Department. Results: Until now, 7 of 17 patients completed the first 6 weeks of the trial. At baseline, the median VAS I score was 54 mm (23-80) and VAS II = 64 mm (33-88). After 6 weeks the median VAS I score was 81 mm (27-89) and VAS II = 78 mm (55-94). In the 5 patients who have completed the 12-week trial, median VAS I = 55 mm (39-80) and VAS II = 67 mm (53-87). Those who finished the trial showed a median Ritchie score of 9.6 at baseline and one of 6.0 at 12 weeks. Adverse events were not observed. Conclusion: These preliminary results suggest improvement of arthralgia in patients with quiescent IBD without side-effects with VSL#3 ($p = 0.1$). This study will probably be completed in September 2003. If preliminary results are confirmed, a randomized placebo-controlled trail is necessary to further confirm the efficacy of VSL#3 in the management of arthralgia in IBD.

Dietary calcium inhibits diarrhea due to enterotoxigenic Escherichia coli infection in humans

I. Bovee-Oudenhoven[1], M. Lettink-Wissink[1], W. van Doesburg[1], B. Witteman[2] and R. van der Meer[1]. WCFS/NIZO food research[1] and Gelderse Vallei Hospital[2], Ede.

In several rat infection experiments, we have shown that dietary calcium inhibits intestinal colonization and translocation of invasive salmonella, probably by strengthening the endogenous microflora. The aim of the present study was to find out whether calcium is also protective against enterotoxigenic Escherichia coli (ETEC) infection, which is an important cause of traveler's diarrhea. This was first tested in our rat model and subsequently verified in a human infection study.
Rats were fed a purified diet with either a low- or a high amount of calcium phosphate and orally infected with ETEC. In addition, a parallel double-blind placebo-controlled intervention study of 3 weeks was performed with 32 healthy men. Subjects largely maintained their habitual diet and consumed either regular (high calcium) milk products or placebo milk products (differential calcium supply was 1040 mg/day). On day 10 subjects ingested a live but attenuated ETEC strain (strain E1392/75-2A), able to induce mild though short-lived symptoms. Primary outcomes studied were infection-induced diarrhea (total fecal output and relative fecal dry weight) and fecal mucin excretion.
In the human study, differential calcium excretion (sum of Ca in urine and feces) was 920 mg/day, indicating good compliance to the study protocol. ETEC induced diarrhea in both groups, as total fecal output doubled and the relative fecal dry weight dropped from 25 to 20%. Additionally, fecal mucin excretion was increased in both groups. All these fecal parameters were completely normalized in the calcium group on the second infection day, in contrast to the placebo group, which recovered on the third infection day. Likewise, supplemental calcium inhibited ETEC colonization and diarrhea in rats.
In conclusion, calcium in milk products improves human resistance to ETEC infection as it inhibits infectious diarrhea.

ORS with a mixture of non-digestible carbohydrates in the treatment od acute diarrhea: a randomised placebo controlled study by the ESPGHAN Working Group on Intestinal Infections*

J.H. Hoekstra[1], H. Szajewska[2], M. Abu Zikri[3], D. Micetic-Turk[4], Z. Weizman[5], A. Papadopoulou[6], A. Guarino[7], J.A. Dias[8], B. Oostvogels[1]. Hieronymus Bosch Hospital[1], 's-Hertogenbosch, Dept Pediatric Gast[2], Warsaw, Children's Hospital[3], Cairo, Maribor Teaching Hospital[4], Dept Pediatrics[5], Beer Sheva, Children's Hospital Athens[6], Dept Pediatrics Naples[7], Facultado de Medicine Porto[8].

Objective: To evaluate the efficacy and safety of a mixture of non-digestible carbohydrates (NDC) as an adjunct to oral rehydration therapy in the treatment of acute infectious diarrhea in children with mild to moderate dehydration in a randomised, double-blind, placebo-controlled multicenter study.
Methods: 144 boys aged 1 to 36 months with diarrhea defined as the passage of three or more watery stools per day for >1 but <5 days; with mild or moderate dehydration (according to WHO criteria) were randomly assigned to receive hypotonic oral rehydration solution (Na 60 mmol/L, glucose 111 mmol/L) with or without a mixture of NDC (soy polysaccharide 25%, a-cellulose 9%, gum arabic 19%, fructo-oligosaccharides 18.5%, inulin 21.5%, resistant starch 7%).
Results: Intention-to-treat analysis did not show significant differences in mean 48 hour stool volume (140 ± 124 gml/kg vs. 143 ± 114 gml/kg; p= 0.41). Total duration of diarrhoea and total duration of diarrhoea in hospital were similar in both groups (130 ± 48 hours vs. 150 ± 79 hours, p= 0.11; and 82 ± 39 hours vs. 97 ± 76 hours, p= 0.24, respectively). There were no significant differences in the duration of hospital stay (111 ± 44 hours vs. 126 ± 78 hours; p= 0.3). Unscheduled intravenous rehydration was similar in both groups (21.4% vs. 16.2%, p= 0.42).
Conclusion: In boys with acute non-cholera diarrhoea with mild to moderate dehydration a mixture of non-digestible carbohydrates was ineffective as an adjunct to oral rehydration therapy.

Gastric acid-suppressive therapy and community-acquired respiratory infections

R.J.F. Laheij, M.C. van IJzendoorn, M.J.R. Janssen, J.B.M.J. Jansen. Dept of Gastroenterology, University Medical Center St Radboud, Nijmegen.

Bacteria and viruses have been detected in stomach of patients during acid-suppressive therapy. The aim of this study was to investigate whether persons using acid-suppressive drugs more often develop community-acquired respiratory infections when compared to those who do not use acid-suppressive drugs.
Overall 700 study subjects were recruited during a single week in December 2002. Information on the prevalence of clinical manifestations of infections and complications in the preceding month was assessed by questionnaire. Furthermore, persons were asked to report antibiotic therapy and physician visits related to possible infection.
Questionnaires were returned by 405 persons (58%). Consumption of acid-suppressive drugs was reported by 91 individuals, of whom 79 used proton pump inhibitors (20%) and 12 H2-receptor antagonists (3%). Overall, 101 (25%) responders reported clinical manifestations of respiratory infection in the preceding month. Persons using acid-suppressive drugs were 2.06 times (95% Confidence Interval(CI):1.2-3.4) more likely to have clinical manifestations of infection than individuals not using acid-suppressive drugs. Persons using acid-suppressive drugs visited 3.72 times (95% CI: 2.1-6.8) more often a physician for an infection and received 4.19 times (95% CI: 2.2-8.1) more often antibiotic therapy in comparison to individuals not using acid-suppressive drugs.
Persons using acid-suppressive drugs more often reported community-acquired respiratory infections in comparison to those who did not use acid-suppressive drugs.

Effect of Black Tea in an ex vivo Model of Infectious Diarrhoea in Piglet Small Intestine

M.J. Bruins[1], J. van der Meulen[2], J.M.M. van Amelsvoort[1], B.J.W. van Klinken[1]. Unilever Health Institute[1], Unilever R&D Vlaardingen and Institute for Animal Science and Health[2], ID-Lelystad.

Tea was associated with anti-microbial properties. Moreover, chewing tea was associated with improved resistance to enteric infections. To test the effect of black tea on acute infectious diarrhoea, black tea was infused to cannulated small intestinal segments of piglets infected with either enterotoxigenic Escherichia coli (ETEC) or Escherichia coli heat-labile toxin (LT).
Spray-dried water extract of black tea-leaves was dissolved in osmotic solution. Black tea solutions with similar osmolality and pH were perfused into ETEC- or LT-infected small intestinal segments of ETEC receptor-positive piglets. After 8-h perfusion, changes in net fluid and electrolyte absorption were determined per cm² intestinal surface. In addition, the capacity of black tea to inhibit LT-induced cytotoxicity was tested in a Vero cell-line. All data were expressed as mean ± least significant difference (LSD).
ETEC significantly impaired the intestinal net fluid absorption (171±112 (-55%) versus 494±112 µL/cm², $P<0.05$) as well as the net sodium and chloride absorption. Black tea significantly improved the ETEC-induced reduction in net fluid (352±112 (-20%) versus 171±112 µL/cm² (-55%), $P<0.05$), as well as net sodium and net chloride absorption. Black tea also significantly restored the LT-induced reduction in net fluid absorption (322±112 (-27%) versus 494±112 µL/cm², $P<0.05$), and net sodium and chloride absorption. In addition, black tea significantly inhibited the LT-induced cytotoxicity towards Vero cells.
Consuming black tea may be beneficial in treating secretory diarrhoea. Black tea probably not only acts against pathogen growth or adhesion, but also against enterotoxins or enterotoxin-induced intestinal electrolyte transport changes and ensuing fluid secretion, although the exact mode of action remains to be elucidated.

Validation of a new portable near patient urea breath test; the Heliprobe system

W.A. de Boer[1], C. Van Alfen[1], S. Badrawi[1], A.H.A.M. Van Oijen[1], J.B.M.J. Jansen, J. Rydén[2]. Dept of Internal Medicine[1], Ziekenhuis Bernhoven, Oss, Netherlands, Noster System AB[2], Stockholm, Sweden.

Introduction: Test&Treat is the evidence-based optimal strategy for the dyspepsia in primary health care. According to the Maastricht guidelines urea breath tests (UBT) are the preferred non-invasive initial Helicobacter test. Usually breath samples need to be mailed to a central facility. We tested a new portable "near patient" 14C-UBT designed for primary care, thus obviating the need to refer the patient.
Aims & methods: Between April 2000 - January 2002 endoscoped patients in whom biopsies were taken to asses Helicobacter status were asked to return for UBT with the Heliprobe system. They received 1 Ci (37kBq) of 14C-urea (Helicap capsle) with citric acid. After 10 minutes the patients exhaled into a breathcard. After saturation it was inserted into the Heliprobe machine. Results take 5 minutes. Infection status was based on number of detected 14C counts per measurement (d). Cut-off values were; infected if d>50, not-infected if d<25, and indeterminate for d-values in-between.
Results: 107 pts participated whereof 1 was excluded due to an indeterminate result. In all pts min 7 biopsies were taken (antrum: 2 histology, 1 culture, 1 CLO. Corpus: 2 histology, 1 CLO). Combined biopsy results served as gold standard against which UBT was compared. Prevalence was 39%. The Heliprobe System was easy to use and results were obtained within 20 minutes. The following results were obtained: Sensitivity 95% (40/42) (95%CI 84-99), and specificity 100% (64/64) (95%CI 94-100). There were no adverse events.
Conclusion: The Heliprobe 14C-UBT system is a very reliable, easy to use, near patient Helicobacter test which can best be used for test&treat in primary health care. It is extremely reliable in patients not taking acid suppressants

A prospective comparison between Magnetic Resonance Cholangiopancreatography and Endoscopic Ultrasonography for the detection of common bile duct stones

J.E. van Hooft[1], F. ter Borg[1], R.M.M.J.J.R. Jaspers[2], M. Ledeboer[1]. Dept of Gastroenterology[1] and Radiology[2], Deventer Hospital.

Magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasonography (EUS) are both accurate non-invasive imaging techniques for the detection of common bile duct (CBD) stones. However, studies comparing MRCP and EUS are almost absent. We report the results of an ongoing prospective study to compare these two methods.

Since April 2002 we included 38 patients (26 female, 12 male, mean age 55(20-80) years) with a suspicion of CBD stones, based on history, laboratory investigation and/or abdominal ultrasound but without an urgent indication for ERCP. They all underwent MRCP and radial EUS. EUS was done by endoscopists having limited experience with EUS for this indication. Both investigations were blinded to one another. When no stones were detected by both methods, patients were followed up for 6 months and if no signs of CBD obstruction had developed by that time, it was assumed that no CBD stones were present. In all other cases, an ERCP with papillotomy and balloon sweep was performed. In 29 cases no stones were detected by both EUS and MRCP. None of these patients developed biliary obstruction during follow up.

In 3 patients stones were found by EUS only (2 confirmed by ERCP), in 2 patients by MRCP only (1 confirmed by ERCP) and in 4 patients by both methods (3 confirmed by ERCP).

Positive predictive values of EUS and MRCP were 71 and 67% respectively; negative predictive values of EUS and MRCP were 97 and 94% respectively. Although EUS performed slightly better, these differrences were not statistically significant.

We conclude that EUS has a diagnostic accuracy with regard to the detection of CBD stones that is comparable to MRCP, even when performed by endoscopists with limited experience. In settings where an urgent MRCP is difficult to obtain or contraindicated, EUS should be considered.

When should we perform an ERCP in the setting of an acute pancreatitis of suspected biliary origin?

H. van Cruijsen, C. Buis, F. Jenniskens, F. ter Borg, H.J.A. Hazenberg.
Dept of Gastroenterology, Deventer ziekenhuis.

There is a paucity of data regarding the parameters that should be used to select patients for ERCP in acute pancreatitis of suspected biliary origin.
We identified 48 patients who underwent an ERCP for suspected biliary pancreatitis between 1997 and 2002, sixteen men and 32 women, median age 63 (21-86) years. At ERCP, stones were found in 25 patients (52%). Patients in whom no stones were found had a longer ICU stay (p=0.047, nonparametric exact test). There were no deaths.
Using logistic regression, the following parameters were not significantly associated with the presence or absence of CBD stones: number of days that the patient had pain before ERCP (median 2, range 1-28), ALAT, ASAT, alk. phosphatase, gallbladder stones and/or dilatation of the CBD on abdominal ultrasound (US). However, the CBD could only be visualised by US in 25 cases and all 4 patients with a CBD diameter > 9 mm had CBD-stones.
A significant association was found for total bilirubin (bili) level (p=0.02) and amylase level (amy) (p=0.04). All 5 patients with amy > 6600 U/l and all 7 patients with bili > 114 mmol/l had CBD-stones. When bili was multiplied by amy (both divided by their upper limits of normal (ULN)), a new variable was created with a high predictive power (p=0.01). Using a cut-off value of 63, a positive predictive value (pv) of 80%, a negative pv of 70%, a sensitivity of 67% and a specificity of 83% were obtained.
We conclude that the product of bilirubin/ULN x amylase/ULN is the most significant laboratory parameter indicating CBD stones in the setting of a suspected biliary pancreatitis.
Otherwise, a very high amylase level (> 6600 U/l), a grossly elevated bilirubine (> 115 mmol/l) or a CBD > 9 mm are reliable indicators of CBD stones. If these features are not present, non-invasive visualisation of the CBD should be attempted first, as there is a high chance of finding no stones at ECP. If no stones are found, our data suggest a more complicated clinical course.

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

Alfabetische lijst van standhouders najaarscongres 2003

K = Kempenhal B = Beneluxhal

ALTANA Pharma	B 20
Alvleesklliervereniging	B 12
AstraZeneca B.V.	B 23
Boston Scientific Microv.	K 1
Cobra Medical BV	K 9
Cook Nederland B.V.	B 22
Danica Nederland B.V.	B 15
Endomed B.V.	K 12
Endotechniek	K 2
Euro Steriel Medical	K 4
E-Wise	K 22
Ferring BV	B 2
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Zambon Nederland B.V.	B 6

Plattegrond expositie

AANMELDINGSFORMULIER VOOR HET LIDMAATSCHAP VAN DE NEDERLANDSE VERENIGING VOOR GASTROENTEROLOGIE

Naam : M/V*
Voorletters :
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o Sectie Kindergastroenterologie

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* doorhalen wat niet van toepassing is.

U kunt zich tevens aanmelden via de website van de NVGE: www.nvge.nl
N.B. Het lidmaatschap loopt per kalenderjaar. Opzeggen dient vóór 1 december te gebeuren.

AANMELDINGSFORMULIER VOOR HET LIDMAATSCHAP VAN DE NEDERLANDSE VERENIGING VOOR HEPATOLOGIE

Naam : M/V*
Voorletters :
Geboortedatum :
Titel :
Specialisme :
Assistent in opleiding voor :

Werkadres
instituut :
afdeling :
straat :
postcode en plaats :
telefoon :
e-mail :

Huisadres
straat :
postcode en plaats :
telefoon :

Doctoraalexamen : ja/neen*; zo ja, welke studierichting:
Datum artsexamen : d.d. . . . . ./n.v.t.*
Inschrijving Specialistenregister : ja/neen*, zo ja, welk:
Speciale interesses op hepatologisch gebied :

geeft zich hierbij graag op als : lid/buitengewoon lid*
contributie: € 16,00 per jaar

Toezending verenigingspost aan huis-/werkadres*.

Datum: Handtekening:

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Nederlandse Vereniging voor Gastro-Enterologie

Sectie Endoscopie Verpleegkundigen en Assistenten

AANMELDINGSFORMULIER LIDMAATSCHAP NVGE / SEVA

Naam : M / V*
Evt. meisjesachternaam :
Voorletters :
Geboortedatum :

Werkadres
Instituut :
Afdeling :
Straat :
Postcode en plaats :
Telefoon :
e-mail :

Huisadres
Straat :
Postcode en plaats :
Telefoon :

geeft zich hierbij op als lid van de Sectie Endoscopie Verpleegkundigen en Assistenten van de Nederlandse Vereniging voor Gastroenterologie tot schriftelijke wederopzegging. *Let wel, het lidmaatschap is persoonsgebonden en niet overdraagbaar. Verenigingspost zal uitsluitend naar uw huisadres worden gestuurd.*

U bent verpleegkundige / doktersassistent(e) anders nl,……*

Datum:…… Handtekening:…….

** aangeven wat van toepassing is.*

☐ Hierbij machtig ik de penningmeester van de Sectie Endoscopie Verpleegkundigen en Assistenten om de verschuldigde contributie, ad. € 15 per jaar, tot wederopzegging automatisch van mijn bankrekening af te laten schrijven. Betaling geschiedt pas nadat u door de eerstvolgende ledenvergadering als lid bent aangenomen.

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Dit formulier sturen naar:
Centraal Secretariaat NVGE (ledenadministratie SEVA)
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