Pathogenesis of IBD W1–W7

W1

CIRCULATING LYMPHOCYTES BUT NOT MONOCYTES HAVE RAISED IL-2 RECEPTOR EXPRESSION IN CROHN'S DISEASE

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In vitro activated lymphocytes and macrophages express interleukin 2 receptor (IL-2r) on their cell membranes. IL2r has been detected on bowel mucosal lymphocytes and macrophages in inflammatory bowel disease and the soluble receptor (sIL-2r) is raised in serum and correlates with disease activity. This receptor may therefore be important in immunopathogenesis. Since there is evidence that circulating monocytes are activated in Crohn's disease, we sought the presence of IL-2r on circulating monocytes in Crohn's disease.

Using two colour Fluorescein activated cell sorter analysis of lysed whole blood, IL-2r expression was measured on both lymphocytes and monocytes in 15 patients with Crohn's disease and in 6 normal controls. Purity of monocytes examined was over 90% using the monocyte marker CD14. Disease activity was measured using the Harvey Bradshaw index (HBI).

Monocytes showed no expression of IL-2r suggesting that this occurs only on arrival at the inflamed bowel mucosa. However, expression of lymphocyte IL-2r was significantly raised in both active and inactive Crohn's disease ($p<0.01$) compared to normal controls and correlated with disease activity measured by HBI ($r=0.7$, $p<0.01$). This study provides further evidence for systemic immune activation in Crohn's disease.

W2

REACTIVE OXYGEN METABOLITES DAMAGE DNA IN INFLAMMATORY BOWEL DISEASE.

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DNA of target cells can be damaged by reactive oxygen metabolites. 8-oxo-7-hydrodeoxyguanosine (8-oxodG) is an important product of oxidative DNA damage which is formed by the reaction of the hydroxyl radical at the C8 position of deoxyguanosine. It can result in base changes and point mutations in replicating DNA and so could play a role in carcinogenesis. 8-oxodG can be measured by high performance liquid chromatography with electrochemical detection. We have used this technique to look for evidence of oxidative damage in the peripheral blood and in full-thickness ileocolonic surgical resection specimens of patients with inflammatory bowel disease (IBD).

Results These are given as the mean and expressed as moles of 8-oxodG / 10^6 moles of deoxyguanosine. Significance was assessed using analysis of variance.

	Blood				Tissue	
	Lymphocytes	(n)	Polymorphs	(n)		(n)
Controls	62	(31)	116	(28)	143	(6)
Ulcerative colitis	84*	(16)	211*	(16)	164	(14)
Crohn's disease	60	(7)	154	(11)	255*	(10)

* $p<0.05$ vs. controls (Fisher's PLSD)

Levels of 8-oxodG were significantly increased in peripheral blood in ulcerative colitis and in gut in Crohn's disease.

Conclusions 1. Increased amounts of 8-oxodG in blood and in tissue provide evidence of oxidative stress in IBD. 2. Since 8-oxodG is a promutagenic DNA lesion, increased production of this in IBD may play a role in the development of cancer in these diseases.

W3

DEPRESSED HLA-DR ANTIGEN EXPRESSION ON CIRCULATING MONOCYTES IN ACTIVE INFLAMMATORY BOWEL DISEASE (IBD).

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Expression of the human leucocyte antigen DR (HLA-DR) on peripheral blood monocytes correlates with the development of infection and predicts outcome after trauma and surgery. We investigated HLA-DR antigen expression on circulating monocytes in IBD patients with respect to disease activity and outcome.

Patients with a clinical relapse of Crohn's disease (CD) or ulcerative colitis (UC) were considered eligible for study if they had not undergone surgery or received immunosuppressants within the previous 3 months. The % positivity and fluorescent intensity (FI) of expression of HLA-DR antigens on monocytes were determined in whole blood samples using dual colour immuno-fluorescence labelling and flow cytometry. Serum alpha 1 acid glycoprotein concentration (αGP) was measured as an index of disease activity. Asymptomatic volunteers served as controls.

Patients were compared according to diagnosis (UC or CD) and serum αGP concentration (0.33-0.88 g/l = inactive; >0.88 g/l = active). Data expressed as mean ± SEM; significance vs control *=$p<0.05$; active vs inactive ‡=$p<0.05$; Student's t test.

	UC	CD	Active	Inactive	Control
	n = 13	n = 5	n = 9	n = 9	n = 15
%	68.5±5.7	67.2±6.1	57.8±4.9*‡	78.5±5.5	73.4±4.0
FI	44.9±2.9	45.2±7.1	39.8±2.5‡	50.2±4.3*	42.3±1.4

Seven patients required surgical intervention within 6 weeks of initial assessment (DR % 52.8±4.5) and 11 received only medical therapy (DR % 77.9±4.5; $p=0.002$).

This study demonstrates that (1) the % of monocytes displaying HLA-DR positivity and the level of HLA-DR expression were significantly decreased in patients with active disease and (2) in patients requiring surgical resection of diseased bowel, the % of monocytes displaying HLA-DR positivity was significantly reduced compared with patients receiving medical therapy alone. The measurement of HLA-DR expression on circulating monocytes may prove useful in predicting outcome of IBD relapses.

W4

T CELL AND MACROPHAGE ACTIVATION INDUCES DESTRUCTIVE CHANGES IN CULTURED HUMAN FETAL SMALL INTESTINE.

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Immunopathological lesions in the small intestine occur in two main types: the *adaptive* lesions seen in conditions such as coeliac disease, characterised by villous atrophy and crypt hyperplasia, and *destructive* lesions, as in Crohn's disease, where mucosal ulceration is a prominent feature. In cultured human fetal small intestinal explants we have previously described mucosal adaptive changes by activating lamina propria CD4+ T cells with pokeweed mitogen (PWM) in the presence of hydrocortisone in the medium. In this study, omitting corticosteroids from the medium we show that similar T cell activation with PWM leads to rapid mucosal destruction with loss of villi, short hypoplastic crypts and epithelial damage. Steroid administration is associated with decreased levels of IL-2 in the culture supernatant. In contrast FK 506 and cyclosporine A completely inhibit T cell activation and the in vitro enteropathy. As demonstrated by sequential immunostaining, in the absence of steroids T cell activation leads to the activation of lamina propria macrophages. Although superoxide anion is produced in increased quantities by these activated macrophages (and inhibited by superoxide dismutase) neither superoxide dismutase nor catalase prevent tissue destruction. N-methyl-l-arginine is also ineffective, making it unlikely that nitric oxide plays a role in tissue destruction. Release of proteolytic enzymes is now the most likely mechanism for mucosal destruction in this model.

W5

PRODUCTION OF COLITIS-SPECIFIC MURINE MONOCLONAL ANTIBODIES USING A NOVEL TOLERISING TECHNIQUE

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Murine monoclonal antibodies that recognise antigens specific to Inflammatory bowel disease (IBD) and not found in normal colon have been generated by tolerising mice to normal colonic mucosal cells and then immunising with cells from inflamed mucosa.

Mice were tolerised by 3 cycles of injection with normal colonic cells followed by IP cyclophosphamide to minimise clonal expansion of B cells reacting to normal colonic antigens. Disease specific monoclonal antibodies were generated by subsequent immunisation with mucosa from Ulcerative Colitis (2 mice), Crohns disease (2 mice) or a pure population of epithelial cells from a case of severe refractory distal colitis where the tolerising cells were from the same patients non-involved right colon. Hybridomas were produced using standard techniques and antibodies screened against frozen sections of colonoscopic biopsies from 15 patients with IBD (11 UC, 4 CD) and 8 control patients without IBD and with normal histology, using an immunoperoxidase technique. Slides were assessed by an experienced histopathologist unaware of the antibodies provenance or the frozen section diagnosis and results analysed with the aim of identifying antibodies reacting to inflamed colon but not to normal colon.

Results: 31 anti-colon antibodies were identified, of which 19 showed a different pattern of staining of inflamed compared to normal mucosa. 6 antibodies stained inflamed tissue but not non-inflamed tissue from IBD patients or normal tissue, while 8 stained both inflamed and non inflamed IBD tissue but not normal colon. 3 antibodies did stain normal colon,but gave stronger staining against inflamed colon. Some antibodies gave mostly apical staining, others mostly cytoplasmic. One antibody stained intracellularly, localising to an area just apical to the nucleus.

These antibodies recognize antigens on cells of IBD patients not found in normal colonic cells. Characterisation of these antigens is in progress and this data may help to a better understanding of cellular mechanisms of antigen presentation, immune recognition and cellular cytotoxicity in IBD.

W6

REACTIVITY OF CLASSICAL ANTI-COLON ANTIBODY WITH RIGHT AND LEFT COLON

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Ulcerative colitis (UC) involves the left side of the colon more commonly than the right. One possible explanation for this is that there are differences in mucosal antigen expression between the two sides, leading to differential activation of immunological mechanisms. Classical anti-colon antibody (CACA) is present in the serum of some patients with inflammatory bowel disease (IBD), reacting in a characteristic pattern with goblet cell mucopolysaccharide. The aim of this study was to determine whether the reactivity of CACA differs between right and left colon.

A conventional 2-stage immunoperoxidase technique was used to screen serum on frozen sections of colonoscopic biopsies obtained from normal and quiescent UC patients. Sera were studied from 53 subjects with UC, 20 with Crohn's disease (CD) and 25 controls (healthy volunteers and non-IBD gastroenterology outpatients). Numbers (percentages) of sera reacting in CACA pattern are shown. Fisher's exact test (2-tail) was used to calculate probabilities.

Results:

Sera	UC Right colon	UC Rectum	Normal Right colon	Normal Rectum
UC (53)	32 (60%)*†	14 (26%)†	36 (68%)**	6 (11%)
CD (20)	7 (35%)	2 (10%)	10 (50%)$	3 (15%)
Controls (25)	7 (29%)x	0 (0%)	16 (64%)**	2 (8%)

* p<0.001 v. UC rectum ** p<0.001 v. normal rectum
† p<0.05 v. controls $ p<0.05 v. normal rectum
x p<0.05 v. UC rectum

UC sera reacted more often with UC tissue than did controls. Otherwise CACA reactivity was similar in each of the 3 study groups; there was a consistent increase in the number of sera staining the right colon relative to the rectum, both for normal and UC tissue. These results suggest that the presence of CACA is relatively non-specific for IBD. However, the differences in reactivity which have been demonstrated between right and left colon may indicate antigenic variation betwen these regions. Such differences could influence the colonic distribution of UC.

W7

REGULATION OF COLONIC EPITHELIAL CELL DERIVED IL-8 SECRETION.

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Cytokines produced by intestinal epithelial cells may be an important signalling system to the adjacent and underlying mucosal immune system. In the present study we asked if intestinal epithelial cells produce the potent neutrophil chemoattractant IL-8. Three colonic adenocarcinoma derived cell lines: T84, HT29 and SW620 were stimulated with either phorbol ester (PMA) or the cytokines: tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1ß), transforming growth factor beta (TGF-ß), interferon-γ (IFNγ) and epidermal growth factor. Confluent monolayers were incubated for 16 hours in the presence of the agonists (all 0.1-300ng/ml, except IFNγ: 1-1000U/ml). IL-8 secretion into the supernatants was determined by ELISA and a bioassay, mRNA production was analyzed by Northern blot hybridization.

As shown in the table below all three cell lines constitutively secreted small amounts of IL-8 which were enhanced in a dose dependent manner by PMA, TNF-α and IL-1ß. Maximal stimulation of IL-8 secretion in HT29 and SW620 cells was 40fold greater than the one achieved in T84 cells. Stimulation of IL-8 secretion was paralleled by increased Il-8 mRNA.

	spont.	stimulated peak IL-8 (ng/ml)		
		PMA	TNFα	IL-1ß
T84	0.3	3.6	3.0	0.5
HT29	1.5	68.6	83.1	42.7
SW620	0.9	79.2	32.7	67.9

TGF-ß, IFNγ and EGF had no effect on IL-8 secretion.

These data demonstrate, that human colon cancer cells constitutively secrete biologically active IL-8. This process is stimulated by proinflammatory agonists and seems to be regulated on the pretranslational level. Intestinal epithelial cells may thus contribute to the development of inflammatory responses in the intestinal mucosa.

Inflammatory bowel disease W8–W14

W8

DETECTION OF MEASLES VIRUS GENOMIC RNA IN CROHN'S DISEASE BY *IN SITU* HYBRIDISATION

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It has been proposed that in Crohn's disease, vascular endothelial cell injury may induce granulomatomous vasculitis. In view of the tropism of measles virus for intestinal microvascular endothelium and the capacity of persistent measles virus infection to induce chronic angiocentric inflammation, we sought evidence of measles virus in Crohn's disease tissues by *in situ* hybridisation.

METHODS: Representative tissue sections (each from 10 cases of Crohn's disease, ulcerative colitis, and non-inflammatory bowel disease, and a positive control of acute measles virus encephalitis) were probed with a biotinylated oligonucleotide-specific for the nucleocapsid-gene of measles virus. From each case, serial sections were treated with either no probe, probe derived from the vector sequence, or RNA digestion prior to hybridisation.

RESULTS: Positive hybridisation for measles virus-RNA was seen in 10:10 cases of Crohn's disease, 4:10 cases of ulcerative colitis and 3:10 cases of non-inflammatory bowel disease, and none of the negative controls. In Crohn's disease the signal localised to giant cells, vascular endothelium in foci of granulomatous and lymphocytic vasculitis, and the centres of lymphoid follicles. Hybridisation was not related to overlying mucosal ulceration. In non-Crohn's disease cases it localised to endothelium and mesenchymal cells, but was unrelated to foci of inflammation.

CONCLUSIONS: Measles virus may cause persistent infection of the intestine. The presence of measles virus-RNA in the characteristic and early lesions of Crohn's disease suggests that measles virus may have an aetiological role in this condition.

W9

PLASMA PROCOAGULANT ACTIVITY IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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Patients with inflammatory bowel disease have an increased risk of venous thromboembolism. The precise mechanisms for this are unknown and no clear pattern of haemostatic abnormality has been established. To investigate the contribution of procoagulant activity to the pathogenesis of inflammatory bowel disease we studied 47 patients [26 with Crohn's disease (16 active, 10 inactive) and 21 with ulcerative colitis (11 active, 10 inactive)] comparing them with 47 age- and sex-matched healthy volunteers. Results are available for von Willebrand factor (vWF), coagulant factor VIII (FVIII:C) and the rate of generation of in vitro thrombin activity, determined by a computer-assisted chromogenic technique.There was a significant shortening of the time taken to generate 50% maximal thrombin activity in seconds (T50/s) comparing patients with inflammatory bowel disease (median [interquartile range] 49 [43-57] s) with controls (54 [49-62] s, p=0.043, n=41). Whereas thrombin generation time was significantly shorter in patients with Crohn's disease (49 [43-53] vs 57 [48-62] s, p=0.027 n=24) the difference was not significant in patients with ulcerative colitis (50 [44-58] vs 51 [49-55] s, p>0.05, n=17). T50 was slightly, though significantly, shorter in patients during active treatment in comparison with pre-treatment and with remission (48 [40-49] vs 49 [47-55] vs 49 [47-51] s, p=0.018, n=21). There was an inverse correlation between T50 and plasma vWF concentration (r= -0.467, p<0.001, n=69), in controls and patients combined. A similar correlation was seen on analysis of preliminary data on FVIII:C and T50. These data have shown that the rate of production of thrombin activity is increased in patients with inflammatory bowel disease, particularly in those with both active and inactive Crohn's disease. The correlation with plasma vWF activity, which may be a marker of vascular damage, indicates that the two processes may be associated. In conclusion, procoagulant activity may contribute to the pathogenesis of inflammatory bowel disease, with particular reference to Crohn's disease.

W10

ANGIOTENSIN CONVERTING ENZYME (ACE) ACTIVITY IS LOWER IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE (IBD) THAN AGE AND SEX MATCHED CONTROLS.

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Angiotensin converting enzyme is a 140 kDa zinc metallopeptidase which in serum is derived from endothelial cells (EC). ACE converts angiotensin I to angiotensin II (AI/AII) by removing the C-terminal his-leu but inactivates bradykinin, enkephalins and substance P.

Decreased serum ACE and increased mucosal AI and AII levels have been previously reported in IBD and rheumatoid arthritis. Using a spectrophotometric method, we have compared serum ACE in IBD with that of age-sex matched controls.

Results expressed as mean ACE level in U/l (SEM) were :

			student's t test value
ulcerative colitis	(n=22)	40.9 (3.3)	p< 0.005
Crohn's disease	(n=16)	37.7 (3.3)	p< 0.001
combined UC / CD	(n=33)	38.2 (2.7)	p< 0.001
controls	(n=33)	53.7(4.0)	

Lower serum ACE in IBD accords with low serum ACE levels in several conditions with a vascular pathogenesis. An explanation may be that decreased serum ACE during inflammation is an appropriate negative feedback response to either mitigate the effects of AII or potentiate those of neurokinins, or that upregulation of EC or tissue ACE may lead to decreased ACE shedding by EC. AII is likely to impair microvascular function via vasoconstriction and the induction of platelet activating factor and platelet derived growth factor.

These findings suggest the role of the renin-angiotensin system and its interaction with kinins, merits further investigation in IBD.

W11

SINGLE PHOTON EMISSION COMPUTERISED TOMOGRAPHY (SPECT); A NOVEL TECHNIQUE FOR IMAGING INFLAMMATORY BOWEL DISEASE USING Tc HMPAO.

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Tc HMPAO white cell scans can be used in the assessment of both extent and severity of inflammatory bowel disease. Although planar imaging techniques provide useful diagnostic information, interpretation may be difficult due to attenuation arising from superimposition of intervening structures such as bone and due to scatter from adjacent structures which may falsely enhance the bowel image. This is particularly important when quantifying bowel activity.

SPECT is a relatively new technique already being applied to imaging other organs e.g.heart, brain. In the abdomen it could allow precise localisation and quantitation of bowel inflammatory activity by providing sectional body images in which the bowel is clearly separated from other structures, particularly the bone marrow.

We report our preliminary experience using this technique for the assessment of inflammatory bowel disease extent and severity in 10 patients with Crohn's disease and 8 with ulcerative colitis. SPECT images were acquired at two hours post reinjection of cells and took approximately 35 mins to perform. Transaxial slices of the abdomen were reconstructed by computer at multiple levels providing accurate localisation of inflammation in both large and small bowel. This promising new technique is non invasive and can be performed using standard nuclear medicine equipment.

W12

AMINO-ACID VERSUS OLIGOPEPTIDE BASED ENTERAL FEEDS IN ACTIVE CROHN'S DISEASE.

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Elemental diets based on either amino-acids or oligopeptides have been used in Crohn's disease to induce remission and improve nutritional status. We have compared amino-acid based E-028 and oligopeptide based Pepti-2000 in a prospective randomised trial. Thirty five patients (E-028 n=19, Pepti-2000 n=16) with active Crohn's disease both clinically (CDAI>150) and on quantitative Tc-99m HMPAO leucocyte scanning, were randomised. The disease was localised to the small bowel in 14, to the colon in 5 and to both sites in 16; randomisation was stratified for disease location. Isocaloric quantities of feed were administered by fine bore nasogastric tube for 28 days, treatment was initiated in hospital but continued at home. The response to treatment was assessed by clinical scoring (CDAI), quantitative leucocyte scanning and laboratory indices of inflammation. Initial assessment was at ten days with final assessment at 28 days.

Results: Thirteen patients entered remission as defined by a reduction in CDAI by 40% or 100 points (E-028 n=8, Pepti-2000 n=5). Seven patients showed some reduction in CDAI but failed to achieve remission (E-028 n=4, Pepti-2000 n=3). Nine patients failed to improve by day ten (E-028 n=5, Pepti-2000 n=4), dietary treatment was therefore terminated and they were treated with steroids or surgery. Six patients withdrew (E-028 n=2, Pepti-2000 n=4) because of vomiting or intolerance of the nasogastric tube. The differences between the diets were not statistically significant.

In conclusion the remission rates in this study are lower than in previous reports. The amino-acid based feed was no more effective than the oligopeptide feed.

H pylori epidemiology and diagnosis W15–W21

W13

QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE: THE INTERACTION OF DISEASE ACTIVITY WITH PSYCHOLOGICAL FUNCTION. G.K. Turnbull, T.M. Vallis, Dept. of Medicine and Psychology, Camp Hill Medical Centre, Dalhousie University, Halifax, Nova Scotia, B3J 2H6, Canada.

Inflammatory Bowel Disease (IBD) is a chronic illness with an unpredictable course of relapses, remissions, and at times hospital admission and/or surgery. Quality of life (QOL), in addition to disease activity, is increasingly recognized as an important factor in patient management. We used a recently validated measure of IBD-specific QOL, the Inflammatory Bowel Disease Questionnaire (IBDQ), to examine the impact of disease activity and psychological function. Psychological measures included the Sickness Impact Profile (SIP), a measure of psychosocial functioning, the Symptom Checklist-90-R (SCL), a measure of psychological distress and the Self-Control Schedule (SCS), a measure of psychological coping. Twenty-two patients (mean age 32), with a mean age of disease onset of 26 yrs (8 males, 14 females) completed the IBDQ, SIP, SCL and SCS. At the same time patients had their disease activity measured with the Van Hees Crohn's Activity Index (n=16) or the St. Mark's Colitis Activity Index (n=6). The psychological and disease activity measures were used to predict disease-specific QOL.

The IBDQ yields a Total score and the following four subscales; Bowel Symptoms, Systemic Symptoms, Emotional Functioning, and Social Functioning. Step-wise multiple regression analyses were used to identify the best predictors of QOL. Of all the measures the SIP, SCL and Disease Activity predicted IBD-specific QOL. Improved psychosocial functioning (SIP) predicted greater overall QOL (IBDQ Total-$p<.004$), fewer bowel symptoms ($p<.05$), and better social functioning ($p<.002$). Greater psychological distress (SCL) and Disease Activity predicted more systemic symptoms (SCL-$p<.01$; disease activity-$p<.03$) and poorer emotional functioning (SCL-$p<.0001$; disease activity-$p<.03$). Disease type, gender, age of onset, and psychological coping (SCS) were not predictive of disease-specific QOL.

Psychosocial functioning (SIP) was the best predictor of IBD-specific QOL. Disease activity only predicted systemic symptoms and emotional functioning, but even here psychological distress (SCL) was a stronger predictor. These data confirm that both disease activity and psychological functioning must be considered jointly when treating IBD patients.

W14

SURGICAL RESECTION RATES IN PAROUS FEMALES WITH DISTAL ILEAL AND COLONIC CROHN'S DISEASE.
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We have compared surgical resection rates in parous females with distal ileal Crohn's (DIC) and colonic Crohn's (CC) with resection rates among all DIC patients (n=227) and CC patients (n=360) treated at The General Hospital inflammatory bowel disease clinics between 1944-79 and 1944-86 respectively. **Methods:** Hospital records of 44 DIC patients and 44 CC patients who had conceived between 1958-92 were scrutinized. 30 of 44 DIC patients and 28 of 44 CC patients had acheived their first pregnancy 8 (mean) years and 6.2 (mean) years respectively, prior to the diagnosis of Crohn's disease. **Results:** Among the 44 parous patients in each disease group resections per patient was negatively correlated with parity. DIC (-0.3681, p=0.014), CC (-0.3036, p=0.045). After a mean follow-up 14.9 years, DIC patients with a history of pregnancy at diagnosis (n=30) recorded decreased resections per patient when compared to all DIC patients: mean(SD) 1.17(0.65) vs 1.52(1.01), p=0.013. Resections per follow-up year were also decreased: 0.076 vs 0.096. After a mean follow-up of 16.5 years CC patients with a history of pregnancy at diagnosis (n=28) recorded decreased resections per patient when compared to all CC patients: mean(SD) 0.68(0.77) vs 1.02(0.77), p=0.029. Resections per follow-up year were also decreased: 0.041 vs 0.069. **Summary:** In patients with DIC and CC, the history of a previous pregnancy is associated with fewer surgical interventions in future years. **Conclusions:** Pregnancy may influence the longterm natural history of Crohn's disease by down-regulating the immune response and/or by retarding progressive fibrous stricturing which leads to repeated surgical intervention.

W15

A 21 YEAR FOLLOW-UP OF HELICOBACTER PYLORI INFECTION - THE "COHORT THEORY" PROVED. D J Cullen, B J Collins, K J Cullen (1), K Christiansen, J Epis, I Surveyor, J R Warren. Royal Perth Hospital and Busselton Population Studies Group (1), Western Australia

Previous studies have shown an increasing prevalence of Helicobacter pylori (HP) antibody titres with increasing age in Western populations. This has been explained either on the basis of gradual acquisition of the infection throughout adult life, or, due to a cohort effect whereby HP was acquired more frequently at a young age in older generations. If the cohort theory is true, then eradication of HP in adults is unlikely to be followed by reinfection at a later date. The Busselton Population Study cohort is a well defined group surveyed during the years 1966-1990. Of this cohort 141 members currently aged 40-65 years had blood sampling in 1969 and December 1990, with 110 (78%) of this same group also sampled in 1978. Sera from all of these samplings was stored and tested for HP antibody using an acid-glycine extract E.L.I.S.A. technique in 1991. Of the sera taken in 1969, 43/141 (30.5%) were positive for HP antibody. Of these 43 HP positive subjects in 1969, 33 were retested on sera taken in 1978 and 32/33 (97%) were HP positive. All 43 HP positive subjects in 1969 were retested on sera taken in December 1990 and 35/43 (81.4%) remained positive. Of the sera taken in 1969, 79/141 were negative for HP antibody. Of these 79 subjects, 63 were retested on sera taken in 1978 and 58/63 (92%) remained negative. All 79 were retested on sera taken in 1990 and 74/79 (93.7%) were still negative. The data provide serological evidence that persistent infection occurs in the vast majority of HP positive adult subjects. The rare acquisition of HP over a 21 year period in this adult group strongly supports the "cohort theory" of HP infection.

W16

HELICOBACTER PYLORI INFECTION IN THE COMMUNITY - A RISK FACTOR FOR PEPTIC ULCER DISEASE BUT NOT DYSPEPSIA. D J E Cullen*, B J Collins, K J Cullen (1), K Christiansen, J Epis, J R Warren, I Surveyor. Royal Perth Hospital and the Busselton Population Study Group (1),Western Australia.

Hospital-based studies of duodenal ulcer (DU) patients have highlighted a strong association between Helicobacter pylori (HP) infection and DU disease. It is not clear, what magnitude of risk of duodenal ulcer faces people in the community who are known to have H.P. infection. The Busselton Population Study cohort is a well-defined group surveyed during the years 1966-1990. Between the years 1969-1990, 171 subjects had blood sampled on 1 to 3 occasions. Of these, 141 had serum stored from sampling in 1969 and 1990 and 151 subjects (88.3%) completed a postal questionnaire about dyspeptic symptoms. General Practitioner records and hospital notes of 164 subjects (95.9%) were reviewed to document peptic ulcer disease, verified by radiology or endoscopy. In 1991 HP antibody titres were determined on all stored serum samples using an acid-glycine extract E.L.I.S.A. technique. The data were analysed using the chi-squared test. Over a 21 year period, 8/53 (15.1%) of subjects with HP antibodies detected (HP +ve) at least once had definite and verified DU during that period, whereas no subjects who were consistently HP antibody negative (HP -ve, N=73) had definite DU ($p < 0.01$). Of 53 HP+ subjects, 10 (18.9%) had definite or possible peptic ulceration (gastric ulcer and DU) compared with 4/73 (5.5%) of HP -ve patients ($p < 0.05$). When subjects with verified peptic ulcer were excluded 16/49 (32.7%) of HP +ve had questionnaire evidence of dyspeptic symptoms, whereas 18/75 (24%) of HP -ve subjects had dyspeptic symptoms (N.S.). These data demonstrate that adults in a rural Australian community who have evidence of HP infection have a markedly increased risk of clinical peptic ulcer disease, with about a 1 in 6 chance of developing an ulcer over a 21 year period. In contrast, when clinical peptic ulcer disease is excluded there is only a trend which is not statistically significant, towards more dyspeptic symptoms in HP +ve subjects.

W17

DIRECT COMPARISON OF ^{13}C AND LOW DOSE ^{14}C AS ISOTOPIC MARKERS IN THE UREA BREATH TEST FOR HELICOBACTER PYLORI

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Both ^{13}C and ^{14}C are widely used as isotopic markers in the urea breath test (UBT) for the diagnosis of, and perhaps quantification of bacterial load in, Helicobacter pylori (H.p) infection. We aimed to see if the two isotopes gave identical results or if inaccuracies in their measurement made correlation less than perfect.

METHODS Eighteen patients (mean age 58 yrs, range 34-77 yrs) underwent simultaneous ^{13}C and ^{14}C UBTs. Subjects received a standardised fatty test meal followed after 10 minutes by 100mg ^{13}C-urea and 46kBq ^{14}C-urea in 50ml water. Breath samples for $^{13}CO_2$ analysis were collected in test tubes using a straw and analysed by mass spectrometry. Samples for $^{14}CO_2$ analysis were collected using a hyamine trapping solution and analysed by scintillation counting. Breath samples were collected at baseline and every 10 minutes for 90 minutes (12 patients) or at baseline and 30 minutes only (6 patients).

RESULTS Correlation between ^{13}C and ^{14}C measurements in 30 minute breath samples was excellent (Pearson Product Moment Correlation Coefficient $r=0.99$ for all values, $r=0.98$ for H.p positive patients [$n=11$] and $r=0.84$ for H.p negative patients [$n=7$]). Individual breath test curves were the same shape for both isotopes. Both tests had 100% sensitivity and specificity when the other was used as the gold standard as expected with the excellent correlation described. For both isotopes the lowest H.p positive value was more than 10 standard deviations from the mean H.p negative value.

CONCLUSION The excellent correlation between values obtained with ^{13}C and low dose ^{14}C means they can be used interchangeably without restandardisation providing a previously standardised UBT protocol is used. The ^{14}C UBT is cheaper and gives acceptably low radiation exposure (7.5×10^{-4}mSv, equivalent to less than one day's natural radiation) so in most situations this test is preferable.

W18

USE OF SERUM PEPSINOGENS AND HELICOBACTER PYLORI SEROLOGY FOR ASSESSMENT OF ANTRAL GASTRITIS IN POPULATION-BASED STUDIES OF GASTRIC CARCINOGENESIS

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We are evaluating the use of serum pepsinogen levels and Helicobacter pylori serology in population-based identification of individuals at increased risk of gastric cancer due to the presence of gastric antral atrophy or intestinal metaplasia (IM). The study involves 487 unselected locally resident males aged 25-65 years. A 10% sample representing the range of pepsinogen levels observed underwent endoscopy and biopsy. Here we examine results from the first 30 examined in order to assess the use of pepsinogens for identification of antral atrophy or IM. Normal gastric histology (n=18) was always associated with 'normal' PGA levels (20-150 ng/ml), PGC levels below 15ng/ml in 16 cases (88.9%), and PGA:C from 3.3-11.4. Only 3 'normal' cases (16.7 %) were Hp antibody positive. Conversely, atrophy or IM in antral or angulus biopsies (n=7) was associated with PGA levels above 150ng/ml in 6 cases (85.7%) and PGC above 15 ng/ml in all cases. Thus the PGA: C range was similar to the 'normal' group (5.7-13.6). All were Hp positive. Thus, for detection of these 'premalignant' gastric lesions:

	Sensitivity	Specificity	PV+ ~	PV- ~
PGA >150 ng/ml	85.7%*	95.0%**	85.7%	95.0%
	SE=0.13	SE=0.05	SE=0.13	SE=0.05
PGC >15 ng/ml	100%	88.9%***	75.0%	100%
	-	SE=0.07	SE=0.15	-

* 1 false positive - Hp negative
** 1 false negative - Hp positive
*** 2 false positives - Hp negative
~ Predictive value (+/- tests)

Low PGA levels (below 20ng/ml), were associated with corpus lymphocytic gastritis (n=2) and corpus IM (n=1). In these cases PGC levels were normal but PGA:C were below 2.0. Our preliminary conclusions are that for identification of 'precancerous' gastric conditions elevated PGA and PGC are markers. Combination tests with Hp serology may reduce false positive/negative rates.

W19

Risk factors for duodenal ulceration in H. pylori positive subjects.

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Background and Aims Duodenal ulcer(DU) is known to be associated with age, male sex, social class, alcohol, smoking and family history. It is also strongly associated with H. pylori infection. However, it is still not known why some individuals with H. pylori infection develop DU and others do not. We have looked at the above as well as childhood factors on the risk of DU in H. pylori positive individuals by means of a case control study. Subjects and methods 284 consecutive subjects undergoing upper gastrointestinal endoscopy for dyspepsia and who were positive for H. pylori infection on biopsy based tests (histology and urease) were studied. Information was obtained on age, sex and ethnic group in 284(78 DUs, 207 controls, mean age 47, range 16-90, 51 West Indians, 64 Asians) subjects, current and past smoking in 245 (74 of the DUs), social class in 225 (70 DUs), family history of PUD in 159 (60 DUs), fathers occupation in 133(58 DUs) and childhood crowding in 128(58 DUs). A further 30 subjects with an abnormal duodenum (either distortion or duodenitis), a history of duodenal ulcer disease, or recent H2 antagonists, but no DU on endoscopy were excluded. Results DU was significantly higher in men 36% vs 16% than women ($p<0.0001$), and also in the <45 year olds, 34% vs 23% in the >45 ($p<.05$). A relationship with family history was also found(29% with DU vs 14%, $p<.03$, relative risk 2.5). There was no associaton with ethnic group (46/169 Caucasians, 15/51 West Indians and 17/64 Asians, NS), or with past or current smoking (48/170 non-smokers vs 26/75 current smokers, NS). Other factors including social class, alcohol, fathers occupation or overcrowding in childhood were not related to the risk of DU. Conclusion In H. pylori positive subjects increased risk of DU is related to age, family history and male sex. Unidentified environmental factors may play a role since ethnic minorities from areas of low DU prevalence have a similar risk to caucasians. H. pylori is believed to be transmitted from person to person. The relationship with family history suggests that either genetic features or more likely properties of the organism itself are also important, due to the lack of effect of ethnic group.

W20

SECRETOR STATUS AND HELICOBACTER PYLORI INFECTION ARE INDEPENDENT RISK FACTORS FOR GASTRODUODENAL DISEASE

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Patients unable to secrete ABO blood group antigens into body fluids (non-secretors) are at increased risk of various bacterial and fungal infections and are also more prone to duodenal ulcer. We investigated the possibility that the increased ulcer risk might be due to increased susceptibility to Helicobacter pylori infection.

We assessed endoscopic abnormalities, secretor status by determination of Lewis blood group phenotype, and presence of H pylori in antral biopsies by histology and commercial urease ('CLO') test in 101 patients (48% male, mean age 45 years, range 19-70) undergoing endoscopy for investigation of dyspeptic symptoms. Of these, 36% had endoscopic gastroduodenal disease (antral gastritis, gastric ulcer, duodenitis or duodenal ulcer), 58% had H pylori infection, and 32% were non-secretors.

Non-secretors were significantly more likely to have gastroduodenal disease than secretors (17/32 v. 19/69: $\chi^2=5.17$, DF=1, p=0.02) as were patients with H pylori infection compared with those without (29/59 v. 7/42: $\chi^2=9.92$, DF=1, p=0.002). However, there was no significant association between secretor status and H pylori infection, which were confirmed to be independent risk factors for gastroduodenal disease by logistic regression analysis. Compared with H pylori -ve secretors (relative risk (RR) = 1.0), the RR (95% confidence intervals) of gastroduodenal disease was 4.1 (1.2-12.8) in H pylori +ve secretors, 3.3 (0.9-12.7) in H pylori -ve non-secretors, and 6.5 (2.1-19.9) in H pylori +ve non-secretors. Overall, the RR for non-secretors relative to secretors was 1.9 (1.2-3.2).

Thus, failure to secrete ABO blood group antigens is a significant risk factor for gastroduodenal disease but the mechanism is not related to susceptibility to H pylori infection and remains to be determined.

W21

DNA FINGERPRINTS OF *H.PYLORI*- INFECTED PATIENTS FREQUENTLY SHOW SUBTYPIC VARIATION BUT ARE HIGHLY STABLE WITH TIME AND TREATMENT

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Helicobacter pylori has a high degree of genomic heterogeneity. We have reported that each individual harbors only one, or uncommonly two strains, and that DNA fingerprints are unchanged after 6-8 weeks of omeprazole (Gastroenterology 1992; 102:829-833 and A70). This study compares DNA fingerprints before and after failed "triple therapy" for *H.pylori*.

Methods: Nine *H.pylori*-infected patients were treated with DeNoltab i qds for 2 weeks, and tetracycline 500mg qds and metronidazole 400mg tds for one week. At least two antral biopsies were taken from each patient before and 6 weeks after completing treatment. Each biopsy was cultured both in selective enrichment medium for *H.pylori* and directly on Skirrow's selective agar, then all isolates were subsequently cultured on brain heart infusion agar. *H.pylori* DNA was isolated and purified, then digested with *Hae* III, electrophoresed, vacublotted, and finally hybridized using a biotinylated cDNA probe prepared from 16S and 23S rRNA of *H.pylori* 11638 NCTC. Isolates were compared using their ribopatterns (DNA fingerprints).

Results: A total of 34 isolates were obtained; there was at least one positive culture before and after treatment for each patient. *H.pylori* isolates from a single biopsy shared the same DNA fingerprint regardless of method of isolation. Paired digest patterns or ribopatterns of *H.pylori* DNA were not affected by treatment with DeNol and antibiotics, although one patient had a different strain cultured after treatment. From all 3 studies, there were 124 isolates from 31 patients: 13 (42%) patients had identical ribotypes in all biopsies, including one patient enrolled in both treatment studies, 14 (45%) had evidence of subtypic variation and 4 patients (13%) harboured two distinct strains.

Conclusions: *H.pylori* from infected persons frequently shows subtypic variation but the *H.pylori* genome is highly stable after failed eradication treatment and a course of omeprazole.

W23

LAPAROSCOPIC VERSUS CONVENTIONAL SURGERY FOR ACUTE APPENDICITIS

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We report a study comparing laparoscopic and conventional surgery in 156 consecutive cases of suspected acute appendicitis. Patients were not randomized; laparoscopy was performed when a suitably-trained surgeon and laparoscopic instruments were available.

Laparoscopic appendicectomy was attempted in 51 patients and was successful in 46 (90%); all conversions to open surgery were due to marked inflammatory adhesions around the appendix and there were no intra-operative complications. Post-operative analgesia requirement after successful laparoscopic surgery was less than after conventional appendicectomy but not significantly different. Re-introduction of normal diet and discharge from hospital occurred at mean 2.0 (±s.d. 0.1) and 3.7 (±s.d. 0.3) days respectively after laparoscopic surgery and 2.4 (±s.d. 0.1) and 4.2 (±s.d. 0.2) days after conventional surgery; these differences are statisitically significant ($p < 0.05$ - Breslow test, $p<0.05$). Post-operative complications were fewer among the laparoscopically-treated patients and wound infections significantly reduced (laparoscopic 1/51 (2%) and conventional 12/97 (13%)).

We conclude that laparoscopic appendicectomy is a practical procedure and has advantages over conventional surgery.

Surgery W22–W28

W22

A PROSPECTIVE ASSESSMENT OF PATIENT BENEFIT OF LAPAROSCOPIC CHOLECYSTECTOMY

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Laparoscopic cholecystectomy has become the procedure of choice for treating symptomatic gallstones and yet few studies have quantified the benefit to the patients over the conventional operation. A prospective study was therefore performed over the period of introduction of the laparoscopic technique to compare the new procedure with a standard cholecystectomy.

60 patients (13 male, 47 female, median age 47 years, range 20-81) with symptomatic gallstones were considered suitable for either laparoscopic or open cholecystectomy and were randomly allocated over a 12 months period to either procedure on the basis of equipment availability. Following surgery a detailed assessment of analgesic requirements, mobilisation, return to normal eating and hospital stay was performed. In addition patient questionnaires analysed the return of home and professional activities. The results were compared between groups using a Mann-Whitney U test and the median values are shown.

Of the 30 patients selected for open surgery 26 underwent cholecystectomy alone. Of the 30 selected for laparoscopic cholecystectomy 24 were successful and 6 required conversion to an open procedure. Comparing the patients undergoing simple open cholecystectomy (n=26) with the patients who had a successful laparoscopic procedure (n=24) showed that the laparoscopic group required less analgesia (1 vs 3 days for opiates injections and 3 vs 8 days of oral pain relief), mobilised quicker (2 vs 3 days), ate sooner (2 vs 4 days), had a shorter in-patient stay (3 vs 6.5 days) and resumed activities at home and work sooner (7 vs 15 days and 15 vs 36 days respectively).

This study has quantified and objectively assessed the patient benefit of a laparoscopic cholecystectomy.

W24

POST-OPERATIVE COLONIC MOTILITY: THE INFLUENCE OF LEFT COLONIC ANASTOMOSIS.

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Post-operative ileus (POI) is most profound and prolonged in the colon, but the type and duration of the intra-abdominal surgery has no effect on its duration in animals. We investigated the influence of operative procedures on colonic motility in the human distal colon.

Eleven patients undergoing recto-sigmoid anastomosis (median age 70: range 47-80 yrs) were compared to 9 patients undergoing laparotomies with no colonic anastomosis (56: 32-65 yrs).

Bowel preparation, anaesthetic and post-operative analgesia were standardised. Microtransducer probes (CTO-3, Gaeltec Ltd) were positioned in the distal colon per-operatively. Colonic manometric activity was recorded continuously using a portable digital data logger (Gaeltec 7MPR) until the first passage of flatus. Quantitative indices of motility were calculated with an automated analysis programme and compared using repeated measures ANOVA (BMDP 5V, Statistical Software Inc).

There was no difference in the total post-operative analgesic doses or duration of surgery between the anastomotic and control groups.

The first return of isolated waveforms (median 1.8, IQR 1-3 hrs vs 4, 1.8-7 hrs) and propagated waves (92, 79-100 hrs vs 73, 72-101 hrs) was similar in both groups, but motor complexes returned earlier in the control group (3, 2-24 hors vs 24, 19-30 hrs; $p<0.05$).

All quantitative indices of motility, except mean amplitude of waveforms, increased significantly with time after surgery in both groups.

The motility index was significantly reduced during the first 72 hrs following surgery in the anastomotic group compared to controls ($p<0.001$), resulting from a reduction of both percentage activity ($p=0.002$) and mean amplitude ($p=0.04$).

Total number of recorded waveforms >12 cmH_2O was comparable between groups but the number >50 cmH_20 was higher in the control group ($p=0.001$).

Flatus was passed at a median of 72 hrs (IQR 45-79) in the control and 94 hrs (81-105) in the anastomotic group ($p=0.05$).

These results suggest that the presence of a left sided anastomosis has a major inhibitory effect on distal colonic motility compared to non-anastomotic surgery of equivalent extent, in the early post-operative period.

W25

ANTERIOR RESECTION SYNDROME: THE PHYSIOLOGICAL BASIS OF PATIENTS' SYMPTOMS.

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The hypothesis tested in this study was that low anterior resection (LAR) for carcinoma leads to abnormalities in the reflex co-ordination of ano-"rectal" function, which could explain why some patients experience problems with continence after operation. Eighteen patients underwent paired tests of ano-rectal manometry before and a median of 3 (1-6) months after operation.

AS pressure:	At rest		"Rectal distension"	
	Pre-op	Post-op	Pre-op	Post-op
2cm from AS verge	56 (28-78)	33 # (26-44)	28 * (10-38)	13 ** (6-20)
1cm from AS verge	63 (55-78)	48 # (36-65)	31 * (12-51)	22 ** (15-33)
0cm from AS verge	51 (42-70)	42 # (29-55)	22 * (7-49)	24 * (15-29)
Volume to produce max. AS inhibition (ml)			100 (50-100)	50 * (40-60)
Max. tolerated volume (ml)			118 (80-165)	60 ** (43-93)

Figures are medians(IQ range) #P<0.03 *P<0.01 **P<0.001 compared with pressure at rest before operation. AS = anal sphincter. Pressure, cm water.

After operation, ten patients experienced minor faecal leakage and 7, urgency of defaecation. Excessive inhibition of the anal sphincter in response to distension of a neo-rectum of low capacity abolishes the pressure barrier that is normally provided by the anal sphincter. These findings do much to explain the defects of anal continence after low anterior resection.

W26

COLONIC POUCH AFTER LOW ANTERIOR RESECTION

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A prospective randomised trial comparing straight low colo-rectal stapled anastomosis(Group A) versus colonic J pouch-low rectal stapled anastomosis(Group B) after anterior resection for rectal carcinoma palpable per anum was performed.

Methods: All patients with a rectal tumour papable per anum submitted for potentially curative low anterior resection were admitted to the trial. Following routine colonic and rectal disection, a 30 mm linear stapler was applied across the anorectal junction and the rectum removed. The patient was then randomised to either group A or B by opening sealed envelopes. All patients randomised to A(n=10: M=7,F=3; median age=60.5 yrs, r=42-86) undergo a stapled low colo-rectal anastomosis using a circular stapler of 31mm diameter. Patients randomised to group B(n=9: M=5,F=4; median age=62 yrs, r=42-83) have a 10 cms long colonic J pouch fashioned with linear staplers before pouch to rectal anastomosis as in group A. A defunctioning ileostomy was used in all cases.

Results: In group A, the median level of the inferior edge of the tumour from the anal verge was 6 cms(r=4-8) and the median distance of the anastomosis from the anal verge was 3 cms(r=2-5). The median frequency of bowel action per 24 hours one month after ileostomy closure was 5(2-15). In group B, the median level of the inferior edge of the tumour from the anal verge was 6.5 cms(r5-8) and the median distance of the anastomosis above the anal verge was 3 cms(r2-4). The median frequency of bowel movement per 24 hours one month after ileostomy closure was 2(r=1/2-5).

Conclusion: The use of the colonic pouch improves stool frequency compared with a straight colo rectal anastomosis after very low anterior resection.

W27

CELLULAR INFILTRATION OF SMALL BOWEL ALLOGRAFTS

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Immunohistological studies suggest that cellular infiltration into the mesenteric lymph nodes and Peyer's patches of intestinal allografts (seen on the first post-transplant day) precedes infiltration of the lamina propria and epithelium.

Lymphocyte suspensions isolated from fully-allogeneic intestinal transplants were stained with monoclonal antibodies and analysed by flow cytometry. Within 24 hours of transplantation at least 57% of lymphocytes within the lamina propria were recipient-derived (see table). Apparent infiltration of the epithelial layer of the graft by recipient derived lymphoid cells was seen on day 1 at low levels, increasing thereafter. There was evidence of impaired functional integrity of the epithelial basement membrane, since suspensions of intraepithelial lymphocytes from both syngeneic and allo-grafts, but not from normal intestine, contained B cells (which should not be found in the epithelial lymphocyte population, implying that cells from the lamina propria have transgressed the basement membrane).

DAY	Epithelium	Lamina propria
1 (n=4)	7.6 ± 4.1	57.3 ± 19.6
3 (n=4)	16.3 ± 6.6	50.6 ± 8.0
5 (n=4)	31.4 ± 12.5	38.3 ± 12.7

Mean percentage (± standard deviation) of recipient derived lymphocytes.

Conclusions

a) Infiltration of the lamina propria of the graft occurs much earlier than previously thought.

b) Although in normal gut the intraepithelial and lamina propria lymphocytes are distinct populations, this is not the case following transplantation and separate analysis may not be justified.

c) Functional impairment of the basement membrane may be an important factor in loss of barrier function following intestinal transplantation.

W28

IS ANAL DILATATION JUSTIFIED?

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Anal dilatation remains a popular choice for the treatment of anal fissure despite the introduction of the lateral sphincterotomy. Since 1984, 182 patients in a single unit have undergone either anal dilatation(AD) or lateral sphincterotomy(LAS). We audited the results of surgery in these patients with particular regard to the incidence of post-operative incontinence. We had a response to postal questionnaire of 80 patients(44%), 57 undergoing AD and 23 LAS. The success rate of AD(86%) was not significantly different to that of LAS(78%). There was a significant difference($p < 0.05$) in the development of some degree of incontinence after AD(49%) versus LAS(4%). 12% of patients treated with AD and no patients treated with LAS developed major incontinence(to liquid or solid). Endoanal ultrasound of patients following AD showed a complex disruption to the internal sphincter which was unlikely to be amenable to surgical repair. Ultrasound following LAS showed a localised defect which could be repaired. In conclusion, lateral sphincterotomy for the treatment of anal fissure is as successful as anal dilatation, causes significantly less incontinence and is easier to repair surgically. We therefore feel that the use of anal dilatation can no longer be justified.

Molecular pathogenesis of liver disease W29–W33

W29

INTRINSIC FIBRINOLYSIS IS DECREASED IN CIRRHOSIS

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Fibrinolysis is reported to be increased in cirrhosis but the mechanism remains unclear. Fibrinolysis is controlled by profibrinolytic factors (tissue plasminogen activator (t-PA), contact factors XII (FXII) and prekallikrein (PK)) and antifibrinolytic factors (plasminogen activator inhibitor (PAI) and Cl-esterase inhibitor (C1EI)). t-PA is endothelially synthesised, FXII, PK and C1EI are hepatic in origin and PAI originates from both tissues.

We have studied global (fibrin plate lysis (GF)) and global intrinsic (dextran sulphate mediated contact activation (DS)) fibrinolytic activity and extrinsic (t-PA), and intrinsic (FXII and PK) fibrinolytic factors in 19 normal controls and 20 patients with cirrhosis (11 Child-Pugh C, 7 Child-Pugh A and 2 Child-Pugh B).

GF activity was similar in both patients (grade C 100.3%, grade A+B 92.1%) and controls (93.0%). DS was significantly decreased in grade C patients (mean 90%) compared with grade A+B patients (mean 119%; $p<0.01$) and controls (mean 125%; $p<0.00001$). Mean plasma t-PA antigen levels were increased in grade C patients (31 ng/ml) compared with grade A+B patients (11 ng/ml;$p<0.05$) and controls (6 ng/ml;$p<0.005$). Mean plasma t-PA chromogenic activity was similarly raised in patients (group C 6, group A+B 5 IU/ml) but different from controls (1 IU/ml; $p<0.001$ both groups). Mean PAI chromogenic activity was similar in all groups (grade C 18, grade A+B 8, controls 6 AU/ml). Mean Factor XII activity was decreased in grade C patients (49 u/dl) compared with controls (90 u/dl; $p<0.0005$) but unchanged in grade A+B patients (70 u/dl). Mean PK activity was decreased in grade C (30 u/dl) and grade A+B patients (46 u/dl) compared with controls (112 u/dl;$p<0.00001$) as was mean ClEI activity (grade C 65, grade A+B 95, controls 117 u/dl; $p<0.0005$ and $p<0.002$ respectively).

Global fibrinolytic activity was normal despite increased t-PA activity levels. The decreased intrinsic fibrinolysis in severe cirrhosis, unaccompanied by a rise in Cl-esterase inhibitor, may be explained by the decrease in factor XII and prekallikrein levels. These changes may be related to reduced liver cell mass.

W30

PLASMA LEVELS OF ACUTE PHASE PROTEINS IN FULMINANT HEPATIC FAILURE AND EFFECT OF LIVER TRANSPLANTATION

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C-reactive protein (CRP) is considered to be the most sensitive and specific marker of the acute phase response. Previous studies have shown that plasma levels, on admission, of another acute phase protein, the protease inhibitor α1-antitrypsin (A1-AT), are normal in patients with fulminant hepatic failure (FHF) who survive. The aim of this study was to determine the serial plasma levels of both proteins in patients with FHF during the course of the illness including the effect of liver transplantation.

Fifty two patients [M:20, F:32] with FHF [39: due to paracetamol overdose (POD) 8: viral hepatitis 5: adverse drug reaction] were studied. On admission: plasma CRP, measured by ELISA, was significantly increased at 18.8 $\pm$ 22.8 μg/ml (vs control: 0.9 $\pm$ 0.5 μg/ml n=20, $p<0.001$). CRP in patients with FHF due to POD was lower than in other aetiologies (14.6 $\pm$ 18.9 μg/ml vs 31.5 $\pm$ 29.7 μg/ml, $p=0.02$). CRP in POD remained lower than in other aetiologies (on day 2: 19.4 $\pm$ 16.6 μg/ml vs 43.0 $\pm$ 47.4 μg/ml, $p=0.023$). On admission plasma A1-AT, determined by chromogenic assay, was significantly decreased, 75.1 $\pm$ 32.3% ($p<0.001$ vs control: 120.9 $\pm$ 16.7%). A1-AT was significantly higher in survivors on day 2 (92.2 $\pm$ 43.9%; n=21 vs 66.3 $\pm$ 31.0%, $p=0.046$; n=19) compared with non-survivors. CRP significantly correlated with A1-AT ($p=0.007$, $r=0.37$) and inversely with PT ($p=0.002$, $r=-0.43$). A1-AT also correlated inversely with PT ($p=0.004$, $r=-0.05$). Liver transplantation caused a significant further increase in CRP (pre: 13.0 $\pm$ 7.8 μg/ml, vs one day after: 94.0 $\pm$ 62.7 μg/ml; $p=0.031$).

In conclusion, patients with FHF are able to produce an acute phase response as evidenced by increases in CRP, and maintenance of this response seems important for survival. The difference in response between CRP and A1-AT is likely to be due to differences in synthesis, formation of protease-inhibitor complexes by A1-AT and in clearance. After liver transplantation there is an acute phase response in the recipient liver.

W31

THE GST1 0 POLYMORPHISM AT THE GLUTATHIONE S-TRANSFERASE 1 LOCUS; PHENOTYPE AND GENOTYPE STUDIES IN PATIENTS WITH PRIMARY BILIARY CIRRHOSIS.

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The liver plays a key role in detoxification of a wide range of xenobiotics. Genetic polymorphism of detoxifying enzymes may render certain individuals susceptible to damage from environmental toxins.

We describe studies designed to test the hypothesis that the null phenotype at the glutathione S-transferase 1 (GST1) locus predisposes individuals to develop primary biliary cirrhosis (PBC).

Liver cytosol from 44 patients with end-stage PBC and 69 control patients without liver disease was studied by starch gel electrophoresis. An initial agarose overlay containing 1-chloro-2,4-dinitrobenzene was followed by a second overlay with iodine-potassium iodide to visualise GST isoenzymes.

There was no significant difference between the groups; the incidences of GST1 *0 in PBC and control groups were 39% and 46% respectively. In the PBC group, all subjects were of the common GST1 *0, GST1 *1, GST1 *2 or GST1 *2-1 phenotypes, while in controls, one subject demonstrated an isoform with an anodal mobility compatible with it being a product of the GST1 *3 allele.

Since the GST1 phenotype might have been altered by advanced liver disease, the polymerase chain reaction, using primers to exon 4 & 5 of the GST1 gene were used to confirm genotype. This demonstrated that in all 13 controls and 11 subjects with PBC tested, GST1 positive and negative genotypes were associated with corresponding GST1 expressing and non-expressing phenotypes respectively. The subject with a putative, rare GST1 *3 phenotype demonstrated a positive GST1 phenotype.

We conclude that deficient glutathione conjugation of environmental toxins is not a factor in the aetiology of PBC.

W32

THE POSSIBLE TUMOUR SUPPRESSOR GENE ON CHROMOSOME 5q FOR HEPATOCELLULAR CARCINOMA IS DISTINCT FROM THE MCC AND APC GENES.

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We have previously reported that a possible tumour suppressor gene is located on the terminal region of the long arm of chromosome 5 (5q35-qter) for hepatocellular carcinoma (HCC) without cirrhosis (Ding et al, BJC, 64, 1083, 1991). Two tumour suppressor genes on chromosome 5 (5q21) for colorectal tumours have been cloned: MCC (mutated in colorectal cancer)(Kinzler et al, Science, 251, 1366, 1991) and APC (adenomatous polyposis coli) (Kinzler et al, Science, 253, 661, 1991).

In this study, we compared the patterns of allele loss (loss of genomic DNA), which may represent tumour suppressor gene loss, in HCC without cirrhosis and colorectal liver metastases (CLM) on chromosome 5q. The probes used were the cDNA probes L5-71 from the MCC gene and 54-D from the APC gene in the region of 5q21, and the probe λMS8 for the region of 5q35-qter. In nine HCC without cirrhosis, the probe λMS8 showed allele loss in 6 out of 6 informative cases, while L5-71 and 54-D showed no allele loss in 5 and 6 informative cases respectively. On the other hand, in seven CLM, 2 out of 3 and 2 out of 4 informative cases had allele loss shown by L5-71 and 54-D respectively, while only 2 out of 5 informative cases had allele loss at 5q35-qter (summarized in the table below).

	L5-71(MCC)	54-D(APC)	λMS8(5q35-qter)
HCC	0/5 (0%)	0/6 (0%)	6/6 (100%)
CLM	2/3 (67%)	2/4 (50%)	2/5 (40%)

In conclusion, the possible tumour suppressor gene on chromosome 5q for HCC without cirrhosis is distinct from the MCC and APC genes.

W33

MYOFIBROBLAST-LIKE CELLS PRODUCE TYP I and III PROCOLLAGEN-mRNAs IN CHRONIC ACTIVE LIVER DISEASE.

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The extent of fibroplasia in chronic active hepatitis can be estimated by light and immunofluorescence microscopy and by measuring the levels of collagen peptides in sera of patients. The rate of collagen biosynthesis is largely determined by intracellular procollagen mRNA concentrations.

Biopsies of five patients suffering from HBsAG-positive chronic active hepatitis and five patients without liver disease were investigated. We used cDNAs for type I and III procollagen to produce (35-S)-labelled RNA fragments complementary to cytoplasmatic mRNAs for the detection of mRNA in liver biopsies by in situ hybridization. Cytoplasmatic mRNA that had hybridized with (35-S)-labelled RNA fragments were visualized by autoradiography as silver grains. Parallel sections were stained with anti-alpha-1-actin using commercially available monoclonal antibodies (Enzo Biochem., N.Y.).

Our study shows increased amounts of type I and III procollagen-mRNAs in chronic active hepatitis in a ratio of 1:1. The cells in which collagen synthesis is enhanced are localized in areas of inflammatory cell infiltration and necrosis. In parallel sections these cells present themselves as alpha-1-actin-expressing cells which can be characterized as myofibroblast-like cells. These are cytokine-mediated transformed Ito-cells.

In situ hybridization technique seems promising to supplement diagnostic procedures for evaluating the activity of liver fibrosis and it should provide additional morphological data to be correlated with serum collagen components.

W35

THE CHRONIC EFFECTS OF ISOSORBIDE-5-MONONITRATE ON PORTAL HAEMODYNAMICS

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Isosorbide-5-mononitrate (ISMN) acutely lowers portal pressure. However, the chronic effect of ISMN on portal haemodynamics is incompletely understood and the development of nitrate tolerance with chronic administration is a possible concern.

Eight patients with histologically proven cirrhosis and oesophageal varices documented at endoscopy underwent haemodynamic assessment before and after one month treatment with ISMN 20 mg bd.

Following one month of ISMN the baseline hepatic venous pressure gradient (HVPG) was unchanged (pre ISMN 19.0 mmHg SE ± 1.2 post 19.9 mmHg SE ± 1.5 p = NS). However, azygos blood flow (AzBF) fell significantly (540 mls/min SE ± 89 to 306 mls/min SE ± 60; p = 0.003) and collateral resistance (CR) increased significantly (44.2 dynes.sec^{-1}cm^{-5} SE ± 8.0 to 91.2 dynes.sec^{-1}cm^{-5} SE ± 21.1; p = 0.029). Acute ISMN challenge after one month of treatment caused a significant fall in HVPG (19.9 mmHg SE ± 1.5 to 16.0 mmHg SE ± 1.8; p = 0,010), but no singificant changes in either AzBf or CR.

This study demonstrates that no significant tolerance to ISMN develops after one month of treatment as shown by the chronic reduction in azygos blood flow and the acute reduction in portal pressure seen on repeat nitrate challenge. Chronic ISMN administration causes a significant reduction in portal-collateral blood flow without reducing portal pressure. The latter however falls acutely following ISMN challenge. These data emphasize the importance of measuring collateral blood flow as well as portal pressure when determining drug effect on the portal-collateral bed.

Portal hypertension W34–W38

W34

SCLEROTHERAPY ALTERS PORTAL VASCULAR REACTIVITY

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Portal hypertension has been shown to induce changes in the reactivity of rat mesenteric blood vessels, with increased sensitivity to 5-hydroxytryptamine (5-HT) and reduced sensitivity to noradrenaline. As injection sclerotherapy of oesophgeal varices may result in a further increase in portal pressure and other haemodynamic changes in portal hypertension, we studied the effect of injection sclerotherapy on vascular reactivity in a portal hypertensive pig model.

Portal hypertension was induced in 10 minipigs by placing a band around the portal vein, following which all animals developed oesophageal varices. Five randomly-selected animals received weekly injection sclerotherapy with 5% ethanolamine oleate from the fifth to the eighth postoperative weeks. Mesenteric veins and arteries were isolated and mounted isometrically in an oxygenated Krebs' solution, and contraction response curves for noradrenaline and 5-HT were determined.

Superior mesenteric veins from sclerotherapy animals showed increased sensitivity to noradrenaline, with a leftward shift in response curves (sclerotherapy pD_2 6.02, control pD_2 6.30) and an increase in maximum contraction of over 100% ($p<0.05$). Superior mesenteric veins from the sclerotherapy group were also more sensitive to 5-HT, but this failed to reach statistical significance. There was no difference in the reactivity of superior mesenteric arteries of the two groups to either agent. There was no correlation between vascular reactivity and the final portal pressure of the animals.

Conclusion: Injection sclerotherapy increases mesenteric venous sensitivity to noradrenaline, and this may play a role in modulating the haemodynamic response to sclerotherapy in portal hypertension.

W36

DO INTRA-HEPATIC PORTO-SYSTEMIC SHUNTS EXIST IN THE NORMAL LIVER ?

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Intra-hepatic porto-systemic shunts have been documented in the cirrhotic liver, resulting presumably from fibrotic and regenerative processes. We present evidence from a new acute microsphere-induced model of portal hypertension suggesting that pressure-dependent shunts exist even in the normal liver.

The maximum pressure induced in haemodynamically-stable anaesthetised rats after intra-portal injection of microspheres (15 to 90 µm diameter) was monitored by intra-splenic and intra-portal cannulae. Mean steady state pressures, obtained after supra-maximal numbers of microspheres, were 13.8 ± 0.3 mmHg (sequential aliquot injections, n=33) and 12.7 ± 0.8 mmHg (bolus injection, n=7), pressure rises of 4.4 ± 0.3 mmHg and 3.4 ± 0.5 mmHg respectively; saline injection produced no pressure changes. There were no significant differences between increases produced by sequential or bolus injections or between differing microsphere sizes. Mean portal pressure rose dramatically to 47.0± 4.2 mmHg when the portal vein was totally occluded at the liver hilum.

This study has demonstrated that, as pressure rises, increasing doses of microspheres do not progressively occlude portal radicles (and further raise pressure). This suggests that microspheres can bypass the normal hepatic microvascular bed of the rat. It is unlikely that this rapid onset 'shunting' occurs outside the liver. Firstly, hours or days are required for extra-hepatic collaterals to become functional. Secondly, application of a portal vein clamp, which excludes intra-hepatic shunts but would leave any extra-hepatic collaterals intact, produces a pressure rise identical to that seen in controls (i.e. animals with no shunts whatsoever). We suggest therefore that as the portal pressure rises, channels greater than 90 µm diameter rapidly open within the normal rat liver to permit direct porto-systemic shunting.

Gastro-oesophageal reflux W39–W43

W37

RELATIONSHIP BETWEEN DUPLEX DOPPLER ULTRASOUND (DDU) MEASUREMENTS OF THE PORTAL VEIN, INDOCYANINE GREEN (ICG) CLEARANCE AND HEPATIC VENOUS PRESSURE GRADIENT (HVPG) IN PATIENTS WITH PORTAL HYPERTENSION

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Portal vein (PV) cross-sectional area (CSA) and PV flow were measured by DDU in patients with alcoholic cirrhosis as part of a trial of chronic drug treatment of portal hypertension. At the same points in the trial that DDU examinations were performed, ICG clearance was assessed, using a single bolus method, and the HVPG was determined from catheterisation of the hepatic vein via the femoral vein. The relationship between these measurements was examined by deriving the correlation coefficient (r).

Results 1. There were significant negative correlations between PV CSA and HVPG ($r = -0.643$; $n = 16$; $p < 0.01$) and PV flow with HVPG ($r = -0.699$; $n = 16$; $p < 0.01$), ie as HVPG increases, PV CSA and flow decrease. 2. There was a significant positive correlation between PV flow and ICG clearance ($r = 0.498$; $n = 15$; $p < 0.05$). 3. ICG clearance also tended to decrease with increasing HVPG, although this did not reach conventional levels of significance ($r = -0.436$; $n = 18$; $p < 0.1$).

Conclusions 1. In established portal hypertension, PV flow (measured by DDU) and total liver blood flow (indicated by ICG clearance) are decreased. This implies that the main determinant of raised portal pressure is increased intra-hepatic resistance. 2. In alcoholic cirrhotic patients with portal hypertension, there is a clear relationship between HVPG and DDU measurements. This suggests the possibility that portal pressure may be assessed non-invasively. 3. There is a good correlation between anatomical (DDU) and physiological (ICG clearance) methods of assessing liver blood flow. This supports the accuracy of these methods and may prove useful in studying the pathophysiology of increased portal pressure and its response to therapy.

W38

TRANSJUGULAR INTRAHEPATIC PORTASYSTEMIC STENT SHUNTS: A PRELIMINARY CLINICAL STUDY

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Introduction: Variceal haemorrhage is the most serious manifestation of portal hypertension. After successful management of a variceal bleed the problem of preventing rebleeding remains. Oral propranolol therapy or repeated injection sclerotherapy are similarly effective, but rebleeding still occurs in up to 60% of patients. Insertion of transjugular intrahepatic portasystemic stent shunts (TIPSSS) has recently been shown to control and prevent gastrointestinal bleeding related to portal hypertension and we report our initial experience of the technique.

Methods: TIPSSS was attempted in 12 patients (8 male, 4 female) for bleeding gastric varices (4 patients), recurrent bleeding from oesophageal varices (5 patients) and bleeding from portal hypertensive gastropathy (3 patients). The TIPSSS technique used was based on previously published methods and was modified as our experience has grown.

Results: A successful TIPSSS procedure with portal pressure reduction to < 15 mmHg was achieved in 10 patients in whom no further haemorrhage was observed; although one patient, admitted 6 months later with reaccumulated ascites, died from variceal haemorrhage before further assessment could be performed. Encephalopathy developed in an elderly patient which improved following a reduction in the diameter of the shunt from 12 to 8 mm. Ascites improved when present. No deterioration in liver function was observed post TIPSSS. One patient with ascites and disturbed coagulation died from uncontrollable haemorrhage related to the procedure.

Conclusions: We have been impressed with the efficacy of the technique in controlling bleeding from gastric or oesophageal variceal or portal hypertension gastropathy, but further studies of appropriate indications, safety and efficacy are required.

W39

FAMOTIDINE IN BENIGN OESOPHAGEAL STRICTURE: A DOUBLE BLIND STUDY

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Benign oesophageal stricture is a complication of long-standing reflux oesophagitis, characterised by symptoms of dysphagia. Good results are usually obtained by a variety of endoscopic dilatation techniques, but continuing acid reflux often leads to recurrence with a need for repeated dilatations. Previous studies (1, 2) with cimetidine have failed to demonstrate any reduction in the need for further dilatations.

Seventy-three patients with benign stricture underwent dilatation during endoscopy and were then randomised to 6 months of treatment with famotidine 40mg bd or placebo. All patients were issued with an alginate/antacid preparation for symptomatic relief if needed. Follow-up endoscopy was carried out after 3 and 6 months, or additionally by patient request, with repeat dilatation if required. Symptom ratings for dysphagia were obtained at each visit.

Fifty patients completed the study; groups were well matched for age, previous history, initial grade of oesophagitis and stricture diameter. Twenty three patients were not evaluated through failure to complete the study (adverse events 9, worsening of symptoms 8, defaulted 4) or protocol violation (2). Patients receiving famotidine had a significantly lower requirement for subsequent redilatation; 11/25 (44%) on famotidine compared with 19/25 (76%) on placebo ($p<0.05$, Chi^2 test).
Both groups showed substantial reduction of dysphagia symptoms; 24/25 (96%) of famotidine-treated patients rated their symptoms 'better' or 'much better', compared with 20/25 (80%) on placebo (N.S).

In conclusion, anti-reflux treatment with famotidine 40mg bd following dilatation of benign oesophageal stricture appears to reduce the subsequent requirement for further dilatation procedures.

1. Ferguson et al, (1979) Br Med J (ii): 472-4
2. Starlinger et al, (1985) Eur Surg Res 17: 207-14

W40

THE IMPORTANCE OF SALIVA IN BENIGN OESOPHAGEAL STRICTURE

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Saliva provides lubrication during swallowing and plays a role in oesophageal acid clearance.
Saliva was collected from 73 subjects under supervision. Whole saliva was collected for 10 minutes before and after administering a saliva stimulant. They belonged to three distinct groups: young volunteers (24 subjects; mean age 28.3 y), elderly volunteers (25; 78.4) and patients with oesophageal stricture (24; 64.8). Volunteers were free of symptoms.
The elderly volunteers group had the smallest volume of resting saliva and the largest number of individuals who had no increase in volume after stimulation, but this was not statistically significant (X^2 test).
In all groups there was only a small and statistically non-significant increment in salivary pH after stimulation.
Bicarbonate concentration rose significantly in both volunteer groups, but not in patients with stricture.
Total bicarbonate content was significantly smaller in the elderly volunteers group. Total bicarbonate content rose significantly after stimulation in all groups except in stricture patients.
Conclusions
The results confirm previous reports that elderly subjects produce less saliva. This becomes important when it is translated into a meagre total bicarbonate content. We speculate that such observation may at least partially account for the tendency of oesophageal peptic strictures to occur at an older age.
Although resting salivary bicarbonate among stricture patients is not different from other groups, there is a more limited rise in this group after stimulation.
Elderly volunteers may have a small volume of resting saliva and a low concentration of bicarbonate but they are able to provide a substantial increase in total bicarbonate content when saliva is stimulated. Stricture patients by contrast seem to have most of their resources (saliva volume and bicarbonate) already utilized before stimulation.

W41

SENSITIVITY OF 24 HOUR OESOPHAGEAL pH MONITORING FOR GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD) IN A DYSPEPTIC POPULATION

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Ambulatory pH profiles may be normal in patients with reflux symptoms but the true sensitivity of these tests is unknown. In this study,24 hour ambulatory oesophageal pH monitoring and a scored symptom assessment were carried out in 96 patients after exclusion of ulcer and gallstones. Patients were categorised thus;
(i) Non reflux dyspepsia (NRD) - no reflux symptoms [n = 42], (ii) Reflux like functional dyspepsia (RFD) - reflux symptoms/normal pH scores, [n = 34] and iii) GORD - reflux symptoms/abnormal pH [n = 20]. pH parameters were compared in all groups.

All parameters of acid reflux were greater in GORD than in the other groups ($p<0.001$). Reflux like symptoms were equal in severity in RFD and GORD. Although RFD patients had parameters of acid reflux within the "normal" range, values were higher than in NRD patients viz:

	NRD	FD	p
Total Acid exposure (mins)	10.2 ± 2.2	16.7 ± 2.8	<0.02
Demeester Score	11.6 ± 0.4	12.9 ± 0.5	<0.05
Pain/reflux event correlation	9.6 ± 4.7%	33.0 ± 7.1%	<0.02
% time pH < 4	0.9 ± 0.2%	1.5 ± 0.2%	<0.05

In 10 RFD patients, pain/reflux event correlation exceeded 50%.

Conclusion: This study suggests that RFD patients may have genuine reflux and that the conventional range for diagnosis of GORD by ambulatory pH monitoring lacks sensitivity.

W43

OMEPRAZOLE TREATMENT OF GASTRO-OESOPHAGEAL REFLUX DOES NOT IMPROVE SYMPTOMS OF NOCTURNAL ASTHMA

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It has been suggested that gastro-oesophageal reflux (GOR) may be an important cause or exacerbating factor in nocturnal asthma. Eleven patients (mean age; 63±9 yrs) with nocturnal asthma and gastro-oesophageal reflux, the latter documented by endoscopy (n=11) and/or 24 hour ambulatory oesophageal pH monitoring (n=9), completed a double blind crossover study (1 week run-in, 4 weeks treatment, 1 week wash-out and 4 weeks cross-over treatment) comparing effect of omeprazole 20 mg od (O) and placebo (P) on asthma symptoms. Asthma diary symptom scores and peak expiratory flow readings (PEFR) did not improve during omeprazole therapy.

		Placebo	Omeprazole
Symptom score	Day	1.0±0.9	0.9±0.7
	Night	1.0±0.6	1.0±0.7
PEFR (l/min)	Waking	262± 86	255 ± 85
	Evening	279± 80	277 ± 78

Bronchodilator inhaler usage was unaffected by omeprazole therapy (P v O; day 1.0±1.7 v 0.8±1.2, night 6.0±4.1 v 4.7±2.8). Treatment of GOR with omeprazole in patients with nocturnal asthma and GOR does not improve asthma symptoms. This suggests that GOR does not often exacerbate bronchoconstriction in nocturnal asthma.

Nitric oxide and gut function W44–W48

W42

THE OESOPHAGEAL RESPONSE TO ACID REFLUX

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Abnormal motility of the oesophageal body is one component in the pathogenesis of gastro-oesophageal reflux disease. The aim of this study was to compare the oesophageal motility response to acid reflux in controls and reflux patients.

Prolonged ambulatory monitoring for a minimum of 18 hours was used to investigate 12 subjects: 6 reflux patients (mean age 39 [26-54] years) and 6 asymptomatic controls (mean age 29 [21-41] years). Equipment consisted of a pressure catheter (4 sensors, 5cm intervals) and 2 pH channels. Motility was analysed manually.

The total number of reflux episodes and mean % time oesophageal pH<4.0 were 22 and 2.5% in the controls, and 110 and 12.5% in the reflux group.

The mean number of contractions in the 2 minute period after reflux onset was significantly higher than in the same period before reflux (3.1 v 2.1, p=0.003) in the control group; this increase was not seen in the reflux group. Mean amplitudes at all oesophageal levels increased significantly following reflux ($p<0.05$), but this response was more marked in the control (mean amplitude increase = 18.3mmHg) than the reflux group (11.4mmHg). There was no significant difference in contraction duration and velocity and % abnormal contractions, before and after reflux in either group.

A significant change in motility following acid reflux was demonstrated in both healthy controls and reflux patients, but this response was more vigorous and more frequent in healthy controls.

W44

INCREASED NITRIC OXIDE SYNTHASE ACTIVITY IN INFLAMED COLON FROM ULCERATIVE COLITIS PATIENTS.

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Nitric oxide synthesis from L-arginine by constitutive calcium-dependent nitric oxide synthase (NOS) has a physiological role in the vasculature, in neuronal activity and gut motility. The induction, by LPS or cytokines, of a calcium-independent NOS, with excessive production of NO, may induce vascular permeability and other inflammatory actions. In the present study, the activity of NOS in colonic tissue from patients with ulcerative colitis (UC) has been investigated.

NOS activity was determined in supernatents (10^4 xg, 20 min) from homogenates of human colon (250 $mgml^{-1}$) as the conversion of [^{14}C]-arginine (27nCi, 30 min, 37°C) to citrulline, a co-product of NO synthesis. In normal uninflamed colonic mucosa and muscle from cancer or polyp resection, NOS activity of 0.10±0.03 and 1.70±0.37 nmol min^{-1} g^{-1} tissue, respectively, (n=6) was abolished *in vitro* by N^G-monomethyl-L-arginine (L-NMMA, 300μM), a specific inhibitor of NOS. In inflamed colonic mucosa from UC patients, NOS activity was markedly increased 7 fold to 0.72±0.21 nmol min^{-1} g^{-1} tissue ($n=4, P<0.01$) and the increase in activity was inhibited by *in vitro* L-NMMA (300μM) but not significantly inhibited by EGTA (1mM).

The marked increase in calcium-independent NOS activity in the inflamed colonic mucosa may account for the mucosal hyperaemia seen in U.C. Furthermore, induction of NOS activity may also be an important pathological factor in mucosal inflammation and the reduced colonic smooth muscle tone of U.C..

W45

ELEVATED NITRIC OXIDE SYNTHASE ACTIVITY IN INFLAMED COLON FROM A RAT MODEL OF COLITIS

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The induction of a calcium-independent nitric oxide synthase (NOS) in the vasculature and leukocytes by LPS or cytokines, leading to excessive NO production, may have a role in inflammation. In the present study the activity of NOS has been determined in inflamed colon from a chronic rat model of colitis.

NOS activity was determined in supernatents (10^4xg,20min) from homogenates of colon (250 mgml^{-1}) as the conversion of [^{14}C]-L-arginine to citrulline (27nCi, 30 min, 37°C). The NOS activity in control colon of 1.41±0.63 nmol min^{-1} g^{-1} tissue (n=6) was inhibited *in vitro* by N^G-monomethyl-L-arginine (L-NMMA, 300μM) a specific inhibitor of NOS, and the calcium chelator, EGTA (1 mM). In inflamed colon taken 24h after induction of colitis by intrarectal trinitrobenzene sulphonic acid (TNB; 60 mg in 30% ethanol), when inflammation was maximum (inflammation score=5.0±0), NOS activity was increased to 4.11±0.54 nmol min^{-1} g^{-1} (n=6, P<0.01) and was inhibited *in vitro* by L-NMMA but not EGTA. After 7 days, when inflammtion was reduced and healing had occurred (score 2.2±0.4), the NOS activity remained elevated (2.3±0.4 nmol min^{-1} g^{-1}, P<0.05) but was calcium-dependent. NOS activity returned to control levels after 2 weeks.

In addition to a calcium-dependent constitutive NOS activity in normal colon, a calcium-independent NOS activity was induced in inflamed colon from a rat model of colitis. NOS induction 24h after TNB may arise from infiltrating leucocytes and inflammatory cytokine generation or exposure to luminal LPS. The later elevation in calcium-dependent NOS activity seen a week after TNB may depend on vascular and mucosal tissue regeneration in the healing colon

W46

cGMP MEDIATES RELAXATION OF DISTAL COLONIC CIRCULAR SMOOTH MUSCLE BY NITRIC OXIDE.

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Nitric oxide (NO) produces smooth muscle relaxation in the cardiovascular system by elevation of intracellular myocyte cyclic guanosinemonophosphate (cGMP) levels. We have previously demonstrated that NO relaxes distal colonic circular smooth muscle (DCCSM) in a concentration dependent manner. We therefore investigated the possibility that cGMP mediates DCCSM relaxation by nitric oxide. Strips of DCCSM from male Wistar rats were mounted on isometric force transducers in organ baths and perfused with oxygenated krebs Henselite solution. Similar but unattached colonic strips were placed beside these in the organ baths. Sodium nitroprusside (SNP) 50uM/l (which liberates NO in solution), nitric oxide gas or control were each added to separate organ baths containing paired colonic strips. The unmounted strips were removed and frozen in liquid nitrogen immediately the force of spontaneous contraction in the mounted strips began to fall. cGMP was measured by radioimmunoassay in tissue following control (0.49mmol/mg, n=6) and was significantly increased by SNP (n=6, mean = 0.58 pmol/mg pr.) and nitric oxide (n=6, mean = 1.85 pmol/mg pr.) (p<0.01, paired t test). An elevation in intracellular cGMP precedes muscle relaxation by nitric oxide.

W47

NITRIC OXIDE MEDIATES CHOLINERGIC RELAXATION OF HUMAN INTERNAL ANAL SPHINCTER SMOOTH MUSCLE *IN VITRO*.

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Nitric oxide (NO) has been implicated as the non-adrenergic, non-cholinergic neurotransmitter producing neurogenic relaxation of the internal anal sphincter (IAS). We have investigated whether NO also mediates human IAS smooth muscle relaxation which occurs in response to cholinergic stimulation.

Small strips (weight: 5-8mg) of IAS circular muscle (n=24 strips from 4 abdomino-perineal resection specimens) were mounted for isometric tension recording in superfusion organ baths at 37°C. Tone was established by loading the strips with a force eqivalent to 1gm but increased spontaneously thereafter, reaching an equilibrium tension of 0.48±0.04 gm/mg tissue after 60 minutes. In this state carbachol, a cholinergic agonist, caused relaxations (dose dependent: 5x10^{-6} - 10^{-4} M), as did electrical field stimulation (EFS: 10 V, 0.5 ms duration, 20Hz, for 1 second). The latter response was nerve mediated as it was abolished by tetrodotoxin (3x10^{-6} M), but the action of carbachol was unaffected by this agent. Relaxations produced by both routes were inhibited by 10^{-5}M nitroarginine, an antagonist of nitric oxide synthase (response to 10^{-5}M carbachol reduced by 69±8%- p<0.05 Willcoxon Signed Rank Test, and to EFS by 100%). This inhibition was reversed by L-arginine (5x10^{-4} M). Oxyhaemoglobin (5x10^{-5}M), which scavenges endogenous NO, completely abolished both relaxations. At these concentrations, nitroarginine and oxyhaemoglobin unmasked small carbachol induced contractions in the muscle strips. The inhibitory effect of carbachol (10^{-5}M) was unaltered by 10^{-6} M hexamethonium, a ganglion blocking agent, but it was abolished by atropine (10^{-6} M), a muscarinic (cholinergic) receptor antagonist.

These results strongly suggest that relaxation of human IAS smooth muscle, which occurs *in vitro* in response to muscarinic receptor stimulation is mediated by NO. The source of NO is, however, unclear and may represent an epiphenomenon, perhaps resulting from activation of vascular endothelial cells. We believe that the effect of cholinergic agonists on the IAS should be reassessed in the light of these findings.

W48

THE NON-ADRENERGIC, NON-CHOLINERGIC NEUROTRANSMITTER WHICH MEDIATES RELAXATION OF THE HUMAN INTERNAL ANAL SPHINCTER IS NITRIC OXIDE.

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Internal anal sphincter (IAS) relaxation is mediated by enteric inhibitory nerves but the identity of the neurotransmiter involved is unknown, except that it is non-adrenergic and non-cholinergic (NANC). Recently, nitric oxide (NO) has been identified as a novel inhibitory neurotransmitter within the gastrointestinal tract and we have explored the role of NO in nerve mediated relaxation of the human IAS.

Small strips of IAS circular muscle (n=72 strips from 12 abdomino-perineal resection specimens) were mounted for isometric tension recording in superfusion organ baths at 37° C. Atropine (10^{-6} M) and guanethidine (3x10^{-6} M) were present throughout to inhibit cholinergic and adrenergic neurotransmission. Tone was established by loading the strips with a force equivalent to 1gm, but increased spontaneously thereafter. In this state, sodium nitroprusside, an exogenous donor of NO, relaxed IAS strips in a concentration dependent manner (10^{-9}- 5x10^{-7} M). Stimulation of the NANC inhibitory nerves (10 V, 0.5 ms duration and 8-20 Hz, for 1 second) produced tetrodotoxin (3x10^{-6} M) sensitive relaxations. The NANC responses were inhibited in a dose dependent fashion by L-nitroarginine (NOARG:10^{-6}-10^{-5}M) and L-monomethyl arginine (L-NMMA:10^{-6}-5x10^{-5} M), both of which are inhibitors of nitric oxide synthase. The nerve mediated relaxations were completely abolished by 10 $^{-5}$ M NOARG and partially inhibited by 5x10 $^{-5}$ M L-NMMA (mean 72.4±2.45% of original NANC relaxation, p<0.05 unpaired t test). The effects of L-NMMA and NOARG were reversed by an excess of L-arginine (5x10^{-4} M) but not its enantiomer, D-arginine. D-NMMA, the enantiomer of L-NMMA had no effect on the tissue. Oxyhaemoglobin (5x10^{-5}M), a scavenger of NO in extracellular media, also abolished the relaxations but methaemoglobin had no such action.

These results strongly suggest that NO is, or is very closely associated with, the neurotransmiter released by enteric inhibitory nerves which mediate relaxation of the human IAS.

Biliary W49–W54

W49

ULTRASOUND (US)-GUIDED PERCUTANEOUS FINE NEEDLE PUNCTURE OF THE GALLBLADDER (PFNP-GB): AN EFFECTIVE TECHNIQUE WITH OCCASIONAL SIDE-EFFECTS. SH Hussaini, C Kennedy*, A Padhani* RH Dowling. Gastroenterology Unit, & *Dept.of Diagnostic Radiology, Guy's Hospital & Campus, UMDS, London.

US guided PFNP-GB, performed for diagnostic and therapeutic reasons, occasionally causes bile leaks and bleeding from the liver but other complications are rare and there are no reports of US changes in the GB following this procedure. Therefore, in 31 consecutive patients undergoing PFNP-GB using a 22FG needle and an intercostal (n=5) or sub-costal (n=26) transhepatic approach for studies of GB bile composition and physical chemistry, we related the time taken to localise and puncture the GB, number of "passes", measurements of GB bile volume aspirated and GB wall thickness before and after puncture, to clinical outcome and frequency of side-effects. RESULTS: The time taken to puncture the GB ranged from 1 to 45 (mean 16.2±SEM 2.3) min while the no. of passes ranged from 1-4 (2.2±0.2) yielding 6-60 (24.9±2.6) ml bile. After puncture, 26 of 31 patients (84%) were asymptomatic and by US the GB wall did not change. However, 2-12h after the procedure, 5 developed RUQ pain which required IM pethidine (50-150mg), associated in 1 with RUQ tenderness and vomiting. None had fever, only 1 had a significant leucocytosis (22 x 10^9/l) and at puncture none had haemobilia, either grossly or by microscopy. In 1 of 5, the GB remained normal by US but the remaining 4 showed echographic changes: (i) thickening of the GB wall (n=4) which increased from <2mm to 4-14 (median 8)mm (ii) an intraluminal mucosal flap (n=1), (iii) a pericholecystic fluid collection of approx 0.5ml (n=1) and (iv) an intraluminal layer of mixed echogenicity. In all 5 patients, the abnormal symptoms and signs settled within 12-24h. In 3, the US changes in the GB wall resolved with 4 wk but in 1, some thickening (3mm) persisted at 6 mo. The reason for these transient US changes in the GB is unknown but may represent oedema/haemorrhage. CONCLUSION: PFNP-GB is a rapid and effective way of sampling fresh GB bile but it carries a 13-16% risk of inducing pain and/or self-limiting US changes in the GB.

W50

EARLY ERCP AND LAPAROSCOPIC CHOLECYSTECTOMY FOR ACUTE GALLSTONE PANCREATITIS.

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Open cholecystectomy is advocated after an attack of gallstone pancreatitis to prevent recurrence whilst ERCP is an effective treatment for common bile duct (CBD) calculi in pancreatitis. With the advent of laparoscopic cholecystectomy (LC) it is imperative that the CBD is clear of symptomatic stones before cholecystectomy. A rational minimally invasive approach to the treatment of gallstone pancreatitis might therefore be ERCP with endoscopic sphincterotomy (ES) when necessary, followed by LC once the CBD is clear.

Fifteen patients (6M, 9F, median age 62 years, range 25-80) with acute gallstone pancreatitis were managed in this fashion. ERCP was performed a median of 4 days after admission (range 1-9). Six patients had CBD stones and these were extracted successfully after ES. LC was undertaken a median of 9.5 days after admission (range 4-34). Mean operating time for ERCP was 30 minutes and for LC 50 minutes. Patients were discharged a median of 2 days after LC (range 1-5) and returned to work at 10 days after discharge 10 days after discharge (range 5-20). There were no complications during this series.

ERCP followed by LC during the same hospital admission appears both feasible and safe and merits further evaluation in a larger series of patients.

W51

GALLSTONE DISSOLUTION WITH MTBE: COMPARISON OF HAND SYRINGE WITH COMPUTERISED PUMP

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Direct instillation of methyl tert butyl ether (MTBE) into the gallbladder by hand syringe is labour intensive. Computerised pump delivery systems are said from in-vitro experiments to reduce labour and increase efficacy, but there is no in-vivo conformation of this. We used the pressure-controlled pump (Lithox Systems Inc., n=10) and compared it with the hand syringe method (n=9). There was no significant difference in the two groups in terms of stone size, stone number or CT attenuation value. Treatment was terminated when complete dissolution was achieved, when no further dissolution was observed or when complications occurred. Cannulation failed in one patient in both groups. In the hand syringe group complete dissolution was achieved in 4 patients vs 3 in the pump group, partial dissolution in 3 vs 5 patients and complications occured in 2 vs 1 patient respectively. Technical failures occurred in 3 pump patients. There was no significant difference in final stone size or number. Mean dissolution time was 355 minutes in the pump group vs 360 minutes in the hand group. We conclude that in our hands the pump was not more efficacious than hand syringe for gallstone dissolution, but was prone to technical failures.

W52

ENDOSCOPICALLY PLACED BILIARY STENTS FOR IMPACTED COMMON BILE DUCT STONES IN THE ELDERLY: RESULTS OF LONG TERM FOLLOW-UP.

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Impacted common bile ducts stones in elderly patients present a difficult clinical problem. Mortality from common bile duct exploration in elderly patients is high, the use of mechanical lithotripsy and dissolution with MTBE are not always successful, and extracorporeal shock wave lithotripsy is not universally available. The aim of this study was to evaluate the long term outcome of the use of endoscopically placed biliary stents for the treatment of impacted common bile duct stones.

The case notes of all patients who received endoscopically placed biliary stents as definitive therapy for impacted common bile duct stones at the John Radcliffe Hospital, Oxford between 1983 and 1992 were analysed retrospectively. 17 patients received stents and data were available on 15. Ten were female and 5 male with a median age of 81 years (range 67 to 93 years). All patients had other significant illnesses which made them poor surgical candidates. 14 patients presented with jaundice of whom 8 had cholangitis. The median number of stones found in each patient was 1 (range 1-8). The median diameter of the largest stone was 2.1cm (range 0.5-3.0cm) and of the common bile duct 2.2cm (range 1.0-3.6cm). All patients had had a failed endoscopic extraction of the stones, or had such large stones that endoscopic removal was judged inappropriate. One patient had failed a two week course of stone dissolution with monooctanoin. The stents used were of the straight type with a lumen diameter of 10Ffrench gague (n=15) and 8Ffrench gague (n=2).

Mean follow-up was for 2.0 years (range 0.3-9.1 years). After stent insertion the mean serum bilirubin fell from 55.1µmol/l (range 5-121) to 33.8µmol/l (range 7-102) and only two patients had a further clinically significant episode of jaundice, both of which were unrelated to the stent (carcinomatosis with liver metastases, n=1; hepatic failure in a patient with pre-existing liver disease, n=1). 8/15 patients died after a mean period of 2.6 years (range 0.2-9.1 years). All these deaths were unrelated to choledocholithiasis.

In elderly patients with impacted common bile duct stones who are unfit for surgery, endoscopically placed biliary stents are a safe, simple, cheap and effective therapy.

Endoscopy W55–W66

W53

GALLSTONES IN CROHN'S DISEASE: AN ALTERNATIVE EXPLANATION

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Disturbances in the enterohepatic circulation of bile salts resulting from terminal ileal disease or resection are believed to lead to lithogenic bile and the raised prevalence of gallstones in Crohn's disease. 250 patients (155 females, 95 males, mean age 44 years) were interviewed and screened by ultrasonography to determine the prevalence of gallstones in a large unselected population of patients with Crohn's disease. 74 (30%) patients had gallstones demonstrated on ultrasonography (n=44), or had undergone cholecystectomy (n=30).

Risk factors for gallstones were examined. Gender, site of disease and site of intestinal resection were not related to the development of gallstones, whereas age (mean age with gallstones 49 years, without gallstones 40 years), duration of disease (mean duration 22 versus 14 years), and previous surgery (91% of patients with gallstones had had laparotomies versus 71% of those without gallstones) were positive risk factors.

The absence of correlation of gallstones with site of disease/resection, and the positive correlation with previous surgery, suggests an alternative pathophysiological mechanism other than ileal dysfunction. We postulate that postoperative gallbladder hypomotility with biliary sludge formation, may be responsible for gallstone formation in patients with Crohn's disease.

W54

PALLIATION OF MALIGNANT BILIARY OBSTRUCTION BY WALLSTENT BILIARY ENDOPROTHESIS: INITIAL EXPERIENCE OF 37 PATIENTS.

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Since February 1991 stainless steel, self-expanding endoprotheses (Wallstents) have been placed in 37 patients with malignant biliary tract obstruction (transhepatic 28, endoscopic 9). Twenty patients (54%) were male and ages ranged from 46 yrs - 89 yrs (median 71 yrs). Twenty-one patients (57%) were considered to have obstruction secondary to pancreatic head carcinoma, 9 (24%) cholangiocarcinoma and 5 (14%) portal lymph node involvement. Five patients (14%) had been previously stented and 2 had reobstructed following bypass surgery; in the remainder this was the primary therapy.

In the early part of the series transhepatic stents were placed by a two-stage procedure after initial passage of a guidewire and internal-external drainage catheter. Since January 1992 we have favoured a one-stage procedure at the initial P.T.C. This was successful in 9 of the last 13 patients, in 3 the stricture could not be passed at the initial sitting and in one cholangiography revealed dual pathology (cholangiocarcinoma and gallstones). Cholangitis was recorded in only one of these 9 patients whereas complications including cholangitis, a bile collection and a subphrenic abscess were recorded in 7 of the 19 patients undergoing prior external or internal-external drainage.

On follow-up two patients have required gastrojejunostomy 3 weeks and 7 weeks post-stenting. Two have developed late cholangitis, one due to debris causing partial stent blockage, successfully cleared by balloon catheter, and one due to stent blockage by tumour ingrowth 2 months after insertion. Stent patency and patient outcome is currently under review.

W55

A PROSPECTIVE AUDIT OF THE APPROPRIATENESS OF UPPER GASTROINTESTINAL ENDOSCOPY USING THE RAND CRITERIA.

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A British strategy to improve the appropriateness of endoscopy has yet to emerge. In the USA, the Rand/UCLA Health Services Utilisation Study (Rand) criteria for appropriate use of endoscopy are widely used. The aim of this prospective study was to score appropriateness of 93 elective endoscopies (59 male, median age 54y (IQR 37-66)) performed for upper gastrointestinal symptoms using the Rand criteria. Subsequently, 60 cases were assessed by a panel of British gastroenterologists (n=16) from 1 health region, each of whom assessed appropriateness individually and without discussion.

RESULTS Using the Rand criteria, 26 (28%) of the 93 endoscopies were judged inappropriate, because of lack of symptoms at the time of endoscopy (n=13), an insufficient trial of therapy (n=11), or other reasons (n=2). The pre-endoscopic diagnoses (% considered inappropriate) in the 93 patients were PU 30 (17%), dysphagia 16 (0%), reflux 13 (31%), haematemesis 5 (0%), dyspepsia-? cause 14 (50%), and others 15 (67%). The British panel, who were unaware of the Rand assessments, subsequently rated 5 of the 60 endoscopies as inappropriate. There was agreement regarding appropriateness of the endoscopy between Rand and the panel in 75% of these 60 procedures. The major areas of disagreement were absence of upper gastrointestinal symptoms at the time of endoscopy (n=6) and an insufficient trial of therapy (n=4), leading to rejection by Rand.

CONCLUSION There appears to be a discrepancy between British panel's and Rand approach to diagnostic endoscopy. The panel were prepared to perform endoscopies regarded as inappropriate by the Rand criteria, because of insufficient treatment or resolution of symptoms. To determine which strategy is more valid, a comparision of their impact on patient behaviour and outcome is needed.

W56

CHANGES IN TREATMENT AFTER OPEN ACCESS GASTROSCOPY AS A MEASURE OF OUTCOME

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We have reviewed the changes in treatment after open access gastroscopy (OAG) as a measure of outcome. Previous studies have used endoscopic findings as an end point. This is a community based study of all patients referred to an unrestricted OAG service in one year, August 1989 to July 1990 inclusive. The changes in treatment over the twelve months after OAG were examined. Of the 954 patients referred complete infomration was retrieved in 715, 75%. A scoring system for medication was devised to quantitate the results.

Prior to OAG 26% of patients received no medication and 28% were on simple antacids. Of those patients receiving treatment prior to OAG, 48% has received treatment for more than four weeks. Thirty-five and a half percent of patients referred has a normal gastroscopy, 35.7% had a major endoscopic finding ie duodenal ulcer, oesophagitis, gastric ulcer or cancer. Twenty-six percent had a minor endoscopic diagnosis ie hiatus hernia, gastritis (no GU), duodenitis (no DU).

Of those patients with a normal gastroscopy, 60% had treatment stopped or reduced for the 12 month period following OAG, in 24% the treatment score was increased. In those patients with a major endoscopic diagnosis 56% had their medication score increased and 25% were unchanged in the 12 month prior following OAG. In those patients with a minor endoscopic diagnosis changes in medication were variable.

In conclusion, following OAG treatment of patients by their General Practitioner appears to change appropriately.

W57

A PROSPECTIVE BLINDED EVALUATION OF THE RAND SYSTEM TO DETERMINE APPROPRIATENESS OF UPPER GASTROINTESTINAL ENDOSCOPY.

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In the USA, insurance reimbursement for upper GI endoscopy is often dependent on satisfying criteria developed by Rand/UCLA using consensus evaluation of clinical scenarios. However, this consensus may be culturally specific. The aim of this study was to compare the evaluation of Rand scenarios for endoscopy by a panel of British gastroenterologists with the original Rand scores of appropriateness.

METHODS A panel of 16 British gastroenterologists from 1 region (medical and surgical consultants and senior registrars) was asked (a) to score the appropriateness of endoscopy for Rand scenarios from 1-9 (1-3 = inappropriate; 4-6 = borderline; 7-9 = appropriate), without knowledge of the Rand assessment, and (b) to score the emphasis and appropriateness of the components of the Rand system.

RESULTS Of 48 case scenarios, 20 (42%) obtained exactly the same median appropriateness scores from the Rand and UK panel assessments. In 14 (29%), a higher median appropriateness score was obtained by Rand and in 14 (29%) a higher median appropriateness score by UK Panel. Overall, the UK panel scored 42 (88%) of the 48 cases in a similar category as Rand, ie appropriate or inappropriate. In a further 48 case scenarios, knowledge of Helicobacter pylori colonisation status or use of non-steroidal, anti-inflammatory drugs did not affect overall assessment of appropriateness of endoscopy by the panel. The panel felt that the Rand criteria, in determining appropriateness for endoscopy, placed appropriate emphasis on assessing the response to therapy, but undue emphasis on results of a prior barium study.

CONCLUSIONS The Rand system to determine appropriateness for endoscopy correlated with the views of a panel of British gastroenterologists in 88% of scenarios, who felt that the American system placed too much emphasis on the results of prior barium meal.

W58

PROSPECTIVE COMPARISON OF SEROLOGY FOR H. PYLORI AND A SIMPLE QUESTIONNAIRE IN SCREENING PRIOR TO ENDOSCOPY

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Background Promising results have been reported using simple question naires and more recently serology for H. pylori in screening for uppe gastrointestinal endoscopy. We aimed to prospectively compare these tests o the same subjects undergoing direct access endoscopy.

Subjects and methods Initial evaluation for the simple questionaire wa carried out on 118 patients (mean age 36, range 22-75) and a cut-off score o less than 8 of a possible maximum of 18 was chosen (sensitivity for detectio of peptic ulcer 88%, specificity 61%). Initial evaluation was also carried ou for H. pylori serology (Porton, Cambridge) on 297 subjects (mean age 47 range 16-90), and a cut-off value of 6.2units/ml was chosen (sensitivity an specificity for detection of infection 98% and 75% respectively) for screenin as part of a strategy of not endoscoping seronegative subjects under the age o 45, who were not taking NSAIDs. Both tests were then carried out on 11 consecutive patients undergoing open access endoscopy.

Results There were 78 normal endsocopies , 29 DUs, 4 GUs, 1 gastri carcinoma and 5 cases of moderate to severe oesophagitis on endoscopy. In th 58 under 45s, there were 41 normal endoscopies, 16 duodenal ulcers and 1 cas of moderate to severe oesophagitis. The serological strategy would hav detected 15/16 (94%) of peptic ulcer disease whilst the simple questionnair would have detected 14/16 (88%) Both would have saved 22/57(39%) o endoscopies. In the combined age groups, the serology strategy would hav saved 26/119 (21%), whilst missing only one duodenal ulcer(1/31= 3% o pathology). The simple questionnaire would have missed 4 DUs, 1 GU, an 1 gastric carcinoma (6/31= 20% of pathology), whilst saving48/119 (40% endoscopies.

Conclusion: The strategy based on serology for H. pylori infection tends to b more sensitive than the simple questionnaire for detecting pathology, an saves a similar number of endoscopies in the under 45 age group. Mor subjects are currently being recruited to confirm these impressions.

W59

SHOULD WE TREAT BACTERAEMIA ASSOCIATED WITH COLONOSCOPIC POLYPECTOMY IN "HEALTHY" PATIENTS?

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Colonoscopy with polypectomy (C&P) has replaced laparotomy with colotomy and polypectomy in the treatment of colorectal polyps. The number of colonoscopies performed each year is steadily increasing. Bleeding and perforation are well documented complications, however, few studies have looked at the less frequent complication of bacteraemia in colonoscopy and especially C&P.

The risk of bacteraemia following colonoscopy and C&P was prospectively assessed by means of blood cultures which were performed prior to and 15 minutes after the procedure. Results of blood cultures were obtained after an incubation period of 24 hours and 7 days. A total of 85 patients underwent 91 colonoscopies, of these, 61 patients had 67 C&P. None of the pre-procedural cultures or the post-procedural colonoscopy only cultures were positive. Three of the C&P patients grew Staph.epidermidis on post-procedural blood cultures taken within 15 minutes of the polypectomy. No patient developed clinical evidence of sepsis during the 24 hours following the procedures. The first pass effect in the liver may be responsible for the low yield of positive blood cultures.

From this study we support the view that no antibiotic prophylaxis is indicated in uncomplicated cases of C&P. However, patients with heart murmurs and with the increasing number of patients with artificial prostheses, a greater awareness is required to institute antibiotic prophylaxis in these high risk groups.

W60

IS SEDATION THE CHOICE OF MOST OUT PATIENTS FOR GASTROSCOPY?

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There is a general assumption that most out patients prefer sedation for gastroscopy. It is not without risk and adds to inconvenience for both patients and staff. 100 consecutive out-patients (50 male), undergoing their first gastroscopy, were offered a free choice in the booking/instruction letter. Their decision to have lignocaine throat spray alone or with intravenous diazepam was stated when reporting to the endoscopy unit. All gastroscopies were performed by the author. Patients received a postal questionnaire one week later and all were returned.

67 patients elected to have spray alone; 33 wanted sedation. 82% of males chose spray alone vs. 52% of females ($p<0.01$). 91% with spray alone said they would make the same choice again. (A subsequent series of 50 other patients undergoing repeat gastroscopy after initial choice of spray alone contained only 3 changing to sedation). 78% with spray alone thought that the procedure was better than expected or acceptable. 4% described it as distressing but all of these said that they would make the same choice again. The main reason given for declining sedation was disruption of the day or need to involve family or friends (69%) but some patients were anxious about needles and impaired consciousness (14%). These reasons outweigh the extra brief discomfort without sedation for most patients.

Advance, free choice has been agreed policy on our unit for 3 years. In the first 3 months of 1992, 731 out patient gastroscopies were performed. Overall, 52% of patients had spray alone but rates varied between the 7 endoscopists; 43-71% for open access cases and 26-58% for clinic derived cases.

Sedation should not be given without considering the view of the patient.

W61

DIAGNOSTIC UPPER GASTROINTESTINAL ENDOSCOPY WITH AND WITHOUT SEDATION: A CONTROLLED STUDY.

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With increasing emphasis on day procedures and open access endoscopy service, sedation prior to diagnostic upper gastrointestinal endoscopy (OGD) has obvious shortcomings.

We conducted a prospective randomised trial comparing the safety and practicality of performing diagnostic OGD with and without prior sedation. All patients referred for OGD during a six month period were considered for the study and were sent a brief description of the procedure with an explanation of the advantages/ disadvantages of sedation one week before the examination. Further explanation was given at the time of OGD.

One hundred and eighty patients consented to the trial, 17 of those failed to complete the questionnaire and were therefore excluded from analysis. The remaining 163 patients were randomised to receive either IV Midazolam 5mg, n=82 or no sedation n=81. All patients received topical throat anaesthesia. Both groups were matched for age, sex, alcohol intake and smoking habits. Seventy eight (95%) of those who received sedation found the examination either not distressful or uncomfortable but tolerable compared to 59 (74%) of those who had no sedation. The majority of patients (92%) were calm and apparently comfortable during the procedure whether or not sedation was given. The mean time needed to complete OGD was similar in both groups (mean ± SEM) 4.9±0.4 min and 4.0±0.3 min respectively. If OGD is to be repeated, over 45% preferred having the examination without sedation, the choice of sedation was independent of age, sex, mood before first OGD, endoscopy duration, or endoscopic diagnosis.

Our results argue against indiscriminate use of sedation prior to diagnostic OGD for the procedure can be performed safely and is well tolerated without sedation.

W62

ENDOSCOPIC FINDINGS IN ASYMPTOMATIC BLOOD DONORS.

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An high seroprevalence of IgG to Helicobacter pylori (HP) in a large asymptomatic blood donors population (42%; 422/1010) has been previously reported. Endoscopy were offered to the first consecutive 182 blood donors. Among these subjects after interviewing (n=162) 128 underwent upper gastrointestinal endoscopy. During endoscopy 4 antral biopsies were taken for CP-Test (1), culture (1), microscopy (Giemsa and Hematoxilin & Eosin staining) (2). Venous blood was collected and IgG to HP were re-assessed.

Results: The endoscopic findings were: 1 gastric cancer, 1 leiomyosarcoma, 19 duodenal ulcers, 5 gastric ulcers, 2 gastric and duodenal ulcers, 20 erosive duodenitis, 6 antral polyps, 14 antral erosions, 42 antral gastritis and 18 endoscopically normal. 121 out of 128 were found to be colonized by HP assessed by Giemsa, CP-TEST, culture and high levels of IgG. In 113 out 121 colonized subjects active on chronic gastritis was found. Seven subjects were found to be not colonized by HP assessed by all the four methods. Interestingly in 3 out of 7 the levels of IgG fall at the time of endoscopy.

Conclusions: This study for the first time has shown the clinical importance of high levels of IgG to HP in screening population. Moreover it highlights the surprisingly high prevalence (20%) of misdiagnosed peptic ulcers in healthy population.

W63

ORIGIN OF PULMONARY ASPIRATE IN PERCUTANEOUS ENDOSCOPIC GASTROSTOMY.

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Following percutaneous endoscopic gastrostomy (PEG), between 2-5% of all patients experience pulmonary aspiration. It is not known whether this is due to pharyngeal secretions or to reflux of gastrostomy feed.

To determine the source of aspirate, 100 mls of barium sulphate (Baritop) were mixed with a 1dm^3 gastrostomy feed and infused over 12 hrs overnight in 29 patients. A plain abdominal film and chest X-ray were taken during the last hour of the barium feed. Aspiration is thought to be more likely when recumbent. The investigation was carried out at 5-10 days after PEG placement, when regular tube feeding had been established.

Eight PEGs were placed for motor neurone disease or multiple sclerosis, 11 for pharyngeal palsy after stroke, 3 after head injury, 4 for carcinoma of the oesophagus or pharynx, 2 for gut hypomotility and 1 for short-bowel syndrome. Three patients with motor neurone disease and 2 with stroke experienced recurrent aspiration prior to PEG placement.

No new cases of aspiration were detected during 2-24 months follow-up. Those previously known to aspirate continued to do so, but did not develop chest infections. Review of chest X-rays failed to demonstrate barium in the bronchial tree of any patient. Barium was noted in the stomach or the intestines of all patients, and in the lower oesophagus of 2 patients, neither of which showed clinical evidence of aspiration.

In conclusion, recurrent aspiration following PEG insertion is not due to reflux of feed, and is likely to be due to pharyngeal secretions, probably mixed with oral food.

W64

ENDOSCOPIC REPAIR OF PERFORATED PEPTIC ULCER WITH A GELATIN PLUG AND FIBRIN GLUE; EXPERIMENTAL EVIDENCE AND CLINICAL EXPERIENCE.

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A new technique of endoscopic treatment of perforated peptic ulcer was investigated in an animal model. These results and those of a pilot clinical study are reported.

A standard 6mm perforation was made in the lesser curve of the stomach of male Wistar rats. Four groups of five rats were randomised to **(1)** no treatment, **(2)** sealing with fibrin glue **(3)** fibrin glue and a gelatin plug and **(4)** suture with omental patch. After five days, the hydrostatic pressures at which the repair failed were compared.

All rats in **(1)** developed peritonitis and 4/5 died. The median pressure in each group at which the repair failed was: **(2)** 4.8cm/H_2O (range 3.0 - 5.0), **(3)** 10.0cm/H_2O (range 6.7 - 11.5) and **(4)** 7.5cm/H_2O (range 2.0 - 10.0). There was no significant difference between groups 3 & 4 but both were significantly better than no treatment or fibrin glue only ($p<0.001$ & 0.02).

Five patients were treated with endoscopic insertion of a gelatin plug and fibrin glue. Recovery was rapid and without complication. Radiological examination at 24hrs with water soluble contrast showed the ulcer to be sealed.

This technique is easy, quick to perform and effective.

Motility W67–W75

W65

KNOT TYING AT FLEXIBLE ENDOSCOPY. K C Lai, CP Swain, F Gong, RS Ratani, G Brown, T Mills.
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Four new knotting techniques were developed by us for use at flexible endoscopy :- 1. half-hitches tied with knot-pusher, 2. self-tightening slip-knot, 3. plastic thread locking device, 4. externally releasable knot. Remoteness from the site of action, access through a small diameter orifice and difficulty in applying lateral traction to tighten knots are the problems met in tying knots at endoscopy. We studied these methods of knot tying and thread control using flexible knot pusher, plastic thread locker, endoscopic sewing machines, elastic bands and different suture material (nylon and silk) in bench experiments on postmortem human stomachs, as well as in live animal and human stomachs. The force required to undo or break the knot was measured using a force-guage. Tightness of endoscopically tied knots (n=140) were compared with hand-tied surgical half-hitch knots.

Increasing the number of half hitches(2 knots, n=10, mean=0.92kg; 3 knots,n=10, mean=0.63kg $p<0.03$) and increasing the diameter of thread(0.12mm nylon, n=10, mean=0.63kg; 0.23mm nylon, n=10, mean=1.05kg $p<0.001$) significantly increased the strength of these knots. There were no statistically significant differences($p>0.1$) between force required to undo or break endoscopically formed knots (mean 0.92kg, range 0.84-1.05kg)when compared with similar hand tied knots formed by a surgeon (mean 0.85kg, range 0.8-0.95kg).The addition of glue (cyanoacrylate or epoxy resin) did not significantly increase knot security. Both the slip knot and thread locker required a significantly ($p<0.05$) shorter time to form a knot compared with the time to tie 3 half hitches.

All four endoscopic knotting techniques were used in survival studies in dog stomachs (n=6) using endoscopic sewing techniques. The externally releasable knot was successfully used to secure a nasogastric tube stitched to patient stomach wall for long term nutrition.

We conclude that knot tying is feasible at flexible endoscopy by a variety of new techniques, can be as secure as surgically hand tied knots and has been used successfully in man.

W66

AUDIT OF 24 PATIENT YEARS OF HOME ENTERAL NUTRITION USING PERCUTANEOUS ENDOSCOPIC GASTROSTOMY. Hull MA, Rawlings J, Hawkey CJ, McIntyre AS, Allison SP, Murray FE. Depts of Therapeutics & Nutrition, University Hospital, Nottingham NG7 2UH, UK.

The long term outcome of patients undergoing percutaneous endoscopic gastrostomy (PEG) is unclear as most series report only short term follow-up. One large long term study reported complications in 100% of patients. All patients undergoing PEG in our hospital are managed by an integrated Home Enteral Nutrition team, comprising gastroenterologist, nutritionist, dietician and nurse. We have instituted (a) a seven day pre-discharge training programme for patients and families, (b) careful follow-up and 'hot line' telephone access to the PEG team for advice and help with problems. Our detailed prospective records allow audit of outcomes and complications encountered in patients treated with PEG since 1988.

RESULTS PEG was inserted in 49 consecutive patients (mean age 64), with CVA 35%, motor neurone disease 27%, malignancy (mainly oropharyngeal) 18% and other 20%. Mean length of PEG feeding was 175 days, and total experience is 24 patient years. Thirty three patients (67%) were able to return home. Four patients died within 30 days, one from PEG-related aspiration pneumonia. Twenty two (49%) of the 45 patients surviving more than 30 days experienced 41 complications, but 21 (53%) of these were resolved by telephone discussion or a dietician home visit. Only 20 (47%) required a hospital visit. The complications were mechanical/tube blockage (n=21), gastrointestinal symptoms such as nausea, reflux, vomiting, constipation or diarrhoea (n=12), and local sepsis, early (n=6) or late (n=2). No episode of sepsis was serious. There were 15 late deaths, one PEG-related (gastric perforation). Six patients subsequently returned to oral feeding.

CONCLUSIONS PEG managed by an integrated team, with emphasis on patient and family education, and availability of a telephone 'hot line' is associated with a lower complication rate than previously described. Most complications encountered were minor.

W67

THE DIFFERENT GROUPS OF FAECAL INCONTINENCE - A PHYSIOLOGICAL STUDY

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277 patients with neurogenic faecal incontinence (FI) were studied electrophysiologically and manometrically. 30.7% had weakness of both anal sphincters (A), 53.8% (B) had a predominant weakness of the external anal sphincter (EAS) and 7.6% (C) a predominant weakness of the internal anal sphincter (IAS). 7.9% had no detectable weakness in either sphincter (D). 23 asymptomatic subjects participated in the study and served as normal controls. The age, duration of FI, the maximum resting pressure (MRP), the pressure increment on coughing (CP) and voluntary contraction 'squeezing' (SQP) in the anal canal were recorded; as were the rectal sensory threshold (RST), the maximum rectal capacity (MRC), the rectal compliance (RC).

	A	B	C	D	Controls	
Age	66	56	68	56	21	(years)
FI	24	24	18	36	-	(months)
MRP	40	100	50	140	120	(cmH_2O)
CP	60	70	120	130	90	(cmH_2O)
SQP	40	60	140	150	150	(cmH_2O)
RST	100	100	110	113	80	(ml)
MRC	245	280	350	350	420	(ml)
RC	3	3	5	4	7	(ml/cmH_2O)

All patients had a reduced RC with higher intrarectal pressures. The majority of them had a weak EAS, whereas the minority who showed a weak IAS had a significant impairment of the RST. Thus, the control of continence is dependent upon rectal function as well as anal sphincter competence. This is a further factor to be considered in the management of FI.

W68

COLONIC MOTILITY DURING ENTERAL NUTRITION. Ana H. Raimundo, J.S.Jameson, J.Rogers, D.B.A.Silk, Department of Gastroenterology and Nutrition, Central Middlesex Hospital, London, UK.

The pathogenesis of enteral feeding- related diarrhoea remains unclear. Results of recent oro-caecal intubation studies in normal subjects pointed to the possibility that the diarrhoea, when it occurs, is likely to result from disturbed colonic rather than small intestinal function. The aim of this study was to determine whether continuous infusion of a polymeric enteral diet evokes an abnormal distal colonic motility response.

Intraluminal pressure recording in the unprepared sigmoid colon was undertaken in seven normal subjects (mean age 24.6 years, 23 - 28) on two separate occasions in random order. Continuous recordings were made for 9 h; 3 h before(fasting) and 6 h during polymeric enteral diet infusion (6.3 gN/L, 1.0 Kcal/ml, at 82ml/h) into either the stomach or duodenum. In addition, five of the subjects underwent a third study of 9 h continuous fasting recording. The pressure records were analysed in ten min periods for the study segment (sum of four channels) activity index (AI = area under the curve, mmHg.min) by fully automated computer analysis.

There was no significant difference in the AI during the infusion period compared to basal values in either the intraduodenal (400 ± 112 vs 640 ± 150 mmHg.min, mean ± SEM) or intragastric (516 ± 53 vs 520 ± 108) diet infusion. In addition, there was no significant difference between AI during intragastric (516 ± 53) and intraduodenal (400 ± 112) diet infusion compared to fasting controls (392 ± 94).

These data show that during intraduodenal or intragastric enteral diet infusion the normal post-prandial colonic response to food is absent, and the colonic pressure activity resembles that of the fasting state.

W69

EFFECT OF CHILLI POWDER ON GUT TRANSIT.

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Food containing spices is commonly thought to alter gastrointestinal function, however there is little evidence to support this belief. In-vitro observations cant be extrapolated to in-vivo and there are no observations using normal meals in healthy humans. Our aim was to investigate the effect of chilli on the transit of a meal through the gastrointestinal tract of normal volunteers.

Seven healthy male volunteers, aged 18-45 y, were given two meals in a random order separated by a week. They took 800 mg cimetidine to remove gastric acid production as this influences the applied potential tomography (APT) technique. This involves attaching 16 surface electrodes around the abdomen and collecting resistivity images to draw a gastric emptying curve. The bland meal was 200 g baked beans and 200 g boiled white rice whilst the chilli-meal had 2 g chilli powder in the beans. They provided end-expiratory breath samples to allow small-bowel transit time to be measured by the breath hydrogen technique. They took 20 radio-opaque markers so that whole-gut transit time (WGTT) could be measured by x-raying all stools passed in the subsequent 60 h.

Gastric emptying was significantly delayed by chilli ; lag time increased from a median of 9 to 20 min ($p<0.05$) and half emptying time increased from a median of 43 to 108 min ($p<0.05$). SBTT increased from a median of 255 to 285 min ($p<0.05$). WGTT was significantly reduced from a median of 47.5 to 36 h ($p<0.05$). Stool weight and frequency were not significantly affected.

Chilli thus has a significant effect on transit through the gut, delaying gastric emptying but speeding whole-gut transit.

W70

MECHANISMS OF ANOREXIA AND VOMITING IN CHILDREN WITH CHRONIC RENAL FAILURE (CRF)

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Anorexia and vomiting can be related to disordered foregut motility and delayed gastric emptying. In CRF anorexia and vomiting cause much morbidity and are yet poorly understood. We recorded foregut motility in 17 children with severe CRF, 13 on conservative medical treatment (MED) and 4 on continuous ambulatory peritoneal dialysis (CAPD). CAPD patients were studied twice (abdomen full and emptied of dialytic fluid). 11 patients (9 MED and 2 CAPD) had severe anorexia and vomiting. Gastro-oesophageal reflux (GOR) was detected by intra-oesophageal pH monitoring, gastric half-emptying time ($T_{\frac{1}{2}}$) of a milk meal by applied potential tomography (APT) and gastric antral electrical control activity (ECA) using surface electrogastrography. Fasting gastrin, neurotensin, glucagon, pancreatic polypeptide and VIP were measured by radioimmunoassay. Gastrin only was elevated in 7/9 CRF patients (49-800 pmol/l, normal <40). GOR was found in 9 symptomatic (7 MED, 2 CAPD, reflux index 5.6% - 22%), but not in asymptomatic CRF patients. Mean gastric $T_{\frac{1}{2}}$ (2SD) in 12 normal controls was 57.5 (27) min. Gastric emptying was delayed ($T_{\frac{1}{2}}$ 107-250 min) in 9 patients, 5 MED and all 4 CAPD with full abdomen, but was normal in 2 asymptomatic CAPD with empty abdomen. Gastric antral ECA (normal frequency 0.05 Hz) was altered in 9 patients (3 tachyarrhythmia at 0.12-0.16 Hz, 2 bradyarrhythmia at 0.03 Hz and 4 unstable ECA), 7 of whom had delayed gastric emptying. 4 previously symptomatic patients (2 MED and 2 CAPD) were restudied after renal transplantation. They had no symptoms and gastric emptying and motility were normal. We conclude that in CRF anorexia and vomiting are related to a complex foregut dysmotility due to an altered humoral environment and/or neural vagal input generated by CRF and its CAPD treatment. We speculate that polypeptide analogues/antagonists may control these symptoms.

W71

THE EFFECT OF CISAPRIDE ON SMALL BOWEL (SB) MOTILITY IN THE IMMEDIATE POST-OPERATIVE PERIOD.

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We have shown (Gastroenterology, 1992; 102:424) that, following colonic surgery, SB motility is highly perturbed, reverting gradually to normality over approximately 60 hrs. The aim of this study was to determine whether the reversion to normality could be enhanced by cisapride (C).

Eighteen patients (median age 68, 52-82 years) undergoing sigmoid colectomy were recruited into a double-blind placebo (P) controlled trial: C or P was given orally on the last pre-operative day and rectally throughout the study. Pre-medication, anaesthetic and post-operative analgesia were standardised. A three sensor naso-jejunal catheter was positioned per-operatively, with sensors located in proximal and distal duodenum and jejunum. Recording continued from 30 minutes after wound closure until passage of flatus. Pressure activity was sampled at 2 Hz and stored on a portable digital recorder (Cavendish Automation). Both visual and semi-automated analysis of the data was undertaken. Statistical analysis for the trends of motor activity was performed using repeated measures ANOVA.

All the measured variables in both groups, tended to increase with time, with the exception of phase III migration velocity which decreased. The change in MMC period was not significantly different ($p=0.9$) between the groups. Phase III duration was initially greater in patients receiving C ($p=0.007$), but, after 60 hours, the difference was no longer significant. With C, phase III migration velocity was more rapid throughout the study ($p<0.001$). The median contractile amplitude of phase III at the distal sensors was greater with C than P, this difference being most apparent after 60 hours. Phase II activity returned at 50-65 hours; this did not differ between the groups. However, there was no significant difference ($p=0.15$) in the timing of the return of bowel sounds between C (median, [interquartile range]: 49, [43-54] hrs) and P (63, [38-82] hrs), or ($p=0.14$) for the first passage of flatus (C: 74, [60-105] hrs; P: 90, [82-109] hrs).

Our data suggest that rectal cisapride given throughout the post-operative period influences SB motility by increasing the amplitude and propagation velocity of phase III contractions, but an improved outcome was not apparent from the clinical observations usually used to assess the duration of post-operative ileus.

W72

CISAPRIDE AND COLONIC MOTILITY FOLLOWING LEFT-COLONIC ANASTOMOSIS: A DOUBLE BLIND PLACEBO CONTROLLED TRIAL.

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Cisapride has been shown to stimulate colonic motility and may prevent post-operative ileus (POI) in animals. We studied the effect of cisapride on the distal human colon during POI.

14 patients undergoing recto-sigmoid anastomosis for localised malignant disease were prospectively randomised to receive cisapride (10mg tds) or placebo, pre- and post-operatively.

Microtransducer probes (CTO-3, Gaeltec Ltd) were placed across the anastomoses per-operatively. Anaesthetic and post-operative analgesic regimes were standardised. Colonic manometric activity was recorded continuously using a portable digital data logger (Gaeltec 7MPR) until the study end-point (first passage of flatus). Quantitative indices of motility were calculated with an automated analysis programme and compared using repeated measures ANOVA (BMDP 5V, Statistical Software Inc).

Cisapride administration did not influence the timing of the first return of isolated waveforms (median 1.5, IQR 0.9-1.8hrs vs 1.8, 1-3hrs), motor complexes (25, 23-31hrs vs 24, 19-30hrs) or propagated activity (63, 50-92hrs vs 92, 51-107hrs) compared to placebo.

All quantitative indices except mean amplitude of waveforms increased significantly with time after surgery in both cisapride and placebo groups.

Cisapride increased the percentage duration of activity compared to placebo ($p=0.002$), reflected in a higher median motility index in the cisapride group ($p=0.03$). This effect was more marked in transducers distal to the anastomoses than those proximal.

Cisapride did not effect mean amplitude of waveforms or increase the number of waves detected >12cmH_2O or >50cmH_2O compared to placebo.

Flatus was passed at a median of 94 hrs (IQR 71-109) in the placebo and 78hrs (55-94) in the cisapride group ($p=0.1$).

Cisapride does not effect the speed of return of colonic activity but increases the percentage duration of activity compared to placebo. It has no major effect on the resolution of post-operative ileus.

W73

HYPERPLASIA OF INTESTINAL MUSCLE FOLLOWS EXPERIMENTAL INTESTINAL NEUROPATHY.

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Background: In addition to hypermotility, an increase of gut smooth muscle thickness is characteristic of human visceral neuropathy but the factors responsible are unknown.

Aim: to study smooth muscle responses to experimental denervation of the rat myenteric plexus induced by Benzalkonium Chloride (BAC).

Methods: Complete myenteric neural degeneration was produced in 6 rats *in vivo*, by serosal application of 0.05%(w/v) BAC to a 5cm segment of jejunum. 0.9% NaCl(BAC vehicle) was used in 6 control animals. Tissue was removed 15 days later, allowed to come to resting length and fixed in formalin. 5μ thick transverse sections were cut, stained with haematoxylin and eosin and neuromuscular morphometry conducted using computerised image analysis.

Results: Control gut: myenteric plexus showed 3.8±0.4 nerve cells and 2.6±0.4 ganglia/mm. Longitudinal muscle thickness was 46.1±9.4μ with 22.9±5.1 nuclei/$10^4\mu m^2$. Circular muscle thickness was 122.6±17.1μ with 63.5±12.9 nuclei/$10^4\mu m^2$.

BAC treated gut: there was a virtual absence of both nerve cells (0.39±0.4/mm) and ganglia (0.27±0.26/mm), ($p<0.05$ vs control). Longitudinal muscle thickness was increased to 137.3±21.1($p<0.05$ vs control) as was circular muscle thickness (327±28.9, $p<0.05$ vs control). In contrast there was no significant difference in the number of nuclei per unit area in either longitudinal or circular muscle layers (29.5±6.3 and 55.8±9.1 nuclei/$10^4\mu m^2$ respectively, $p>0.05$ vs control).

Conclusion: Intestinal denervation produces smooth muscle hyperplasia without evidence of hypertrophy despite increased muscle work. The myenteric plexus may exert a negative trophic effect on the intestinal smooth muscle cells although the factors responsible for such growth remain to be determined.

W75

THE COLONIC RESPONSE TO FOOD IS COMPOSED OF MULTIPLE CHANNEL CONTRACTIONS WHICH CAN BE BLOCKED BY MEBEVERINE.

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The colonic response to a meal is often used to assess drug effects on motility. The aim of this study was to determine whether analysis of the pattern of sigmoid contractions could provide a clearer index of the meal response. Two studies were carried out in 16 volunteers employing a multi-lumen catheter with perfused rectosigmoid side holes. In study one motility recording was carried out for five hours with a standard fatty meal given after 180 mins.

Traces were analysed pre/postprandially for motility index (MI), contractions in a single recording channel (SCC) and those simultaneously in multiple channels (MCC).

Results :-	preprandial	postprandial
MI	17285(2297)	298880(3090)*
SCC/hr	65(10)	56(11)
MCC/hr	9(3)	57(9) **

Mean(sem) *=p<0.05 ,**=p<0.01 from preprandial

Postprandially there was a significant rise in the motiltiy index resulting from a massive increase in the number of MCC's whilst there was a concomitant decrease in the SCC's.

In a second study an infusion of an anti-spasmodic drug, mebeverine hydrochloride (75mg), into the sigmoid colon prevented the significant rise in postprandial motility by abolishing the increase in the MCC's. Mebeverine had no effect on the SCC's.

In conclusion our results demonstrate that the colonic response to a meal consists of alterations in patterns of rectosigmoid contractions and that MCC's may be a more sensitive indicator of both the meal effect and the effectiveness of drugs used in the modulation of colonic motility.

Colorectal W76–W85

W74

EFFECT OF SIMULATED RAPID GASTRIC EMPTYING ON THE LOWER OESOPHAGEAL SPHINCTER

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Patients with gastro-oesophageal reflux have been shown to have abnormal gastric motility. The influence of duodenal responses to changes in gastric emptying patterns upon the lower oesophageal sphincter has not been explored.

Fourteen fasted subjects (10M, 4F; median age 28y, range 24-51y) were intubated with a naso-duodenal tube and a water-perfused manometry catheter. Lower oesophageal sphincter pressure vector volumes and sphincter length were calculated from station pull-through manometry in the basal state and following 15 minute duodenal instillations with 15% dextrose at 3ml/min, 15% dextrose at 9ml/min and isotonic saline at 9ml/min. Ethical Committee approval was obtained.

There was no significant difference between lower oesophageal sphincter pressure vector volumes (mmHg.mmHg.mm) in the fasted state [10073 (5984-13108)] + and those following dextrose at 3ml/min [10251 (4956-12552)] or saline at 9ml/min [7869 (6467-14773)]. Dextrose at 9ml/min caused a large reduction in vector volume [1247 (282-2527)]**.

Total length of sphincter (mm) in the fasted state [40 (30-50)]++ fell following duodenal dextrose at 9ml/min [30 (20-40)]*. Abdominal length of sphincter also fell but did not reach significance.

15% dextrose instilled into the duodenum at supranormal rates causes a significant fall in lower oesophageal sphincter pressure vector volumes and total length of sphincter. Preliminary results suggest that this response is enhanced in patients with gastro-oesophageal reflux disease.

\+ Median and Inter-Quartile Range
++ Median and Range * $p < 0.05$, ** $p < 0.01$, Wilcoxon

W76

QUALITY OF LIFE AFTER RECTAL EXCISION FOR CARCINOMA

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The aim of this study was to investigate whether quality of life after potentially curative rectal excision for carcinoma is related to the level of the anastomosis. Four groups of patients were studied, of similar age and duration of follow up after operation. Each patient completed a questionnaire on bowel function which included a psychological (HAD) anxiety (A) and depression (D) assessment (Table).

Level of anastomosis above HPZ	Colo-anal 0-2 cm	Colo-rectal <4cm	Colo-rectal >4cm	Permanent Colostomy
No./patients	15	14	12	28
Bowel freq. /24h	5 * (2-8)	3 (1-8)	2 * (1-4)	2 * (1-3)
Urgency	5 *	4	0*	0 *
Faecal leak	8 *	8	2 *	1 *
HAD A score	4 (0-14)	3.5 (0-13)	2 (0-8)	3.5 (0-12)
HAD D score	1 (0-6)	1 (0-11)	1 (0-4)	3 (0-12)

(Median and range. * P < 0.01, HPZ= High pressure zone)

Thus, quality of life is related to the level of the anastomosis. Nevertheless most patients with very low resections were still satisfied with the outcome.

W77

ILEO-ANAL ANASTOMOTIC STRICTURE AFTER RESTORATIVE PROCTOCOLECTOMY

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The aim of this study was to determine what factors may be responsible for the development of an ileo-anal anastomotic stricture (IAAS) after restorative proctocolectomy in a consecutive series of 115 patients. Patients who eventually needed a permanent ileostomy (9.6%) and one patient with familial polyposis who developed a stricture due to a desmoid tumour, were excluded from the analysis. Of the remaining 102 patients 39 developed a stricture (38%), which was defined as the need for dilatation under anaesthetic on at least two occasions.

	No stricture	Stricture	
Number of patients	63	39	
Handsewn anastomosis	13	5	
25 mm stapler anastomosis	10	13	*
28 mm stapler "	39	20	
31 mm stapler "	1	1	
One-stage operation	25	10	
Two-stage operation	38	29	
Pelvic sepsis	13	14	*

*P< 0.05 Fisher exact test

Although the incidence of anastomotic stricture was high at 38%, failure of the operation was attributed to IAAS in only one patient (0.9%). All patients were successfully managed by simple dilatation. Two factors were found to be significantly associated with the development of IAAS: use of the small (25 mm) stapling gun and the pelvic sepsis. We suggest that a 28 mm or 31 mm stapler should be used if possible when a stapled ileal-pouch-anal anastomosis is constructed.

W78

CHANGES IN COLONIC pH AND BREATH HYDROGEN PRODUCTION FROM INGESTION OF DIETARY FIBRE.

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Colonic pH is determined by short chain fatty acids (SCFA) generated from the fermentation of dietary fibre. Different fibre sources vary considerably in their fermentation. To test this hypothesis, subjects were fed three different meals on three separate occasions. End products of bacterial metabolism, SCFA induced pH change and breath hydrogen, were measured.

Method: The three test meals were: 1) complex polysaccharide free (control, fibre free meal) of cheese and yoghurt, 2) 20g of soluble nonabsorbable polysaccharide (lactulose), 3) 20g mixed dietary fibre (wholemeal bread). Dietary fibre was withheld from the diet for 24 hours prior to each study. Large bowel pH was measured using a radiotelemetry pH capsule, and the capsule was localised within the bowel using a radio detector. Breath hydrogen samples were obtained hourly.

Results: Breath hydrogen (H_2) production rose after lactulose and bread meals, but not after the control meal. Peak mean H_2 values after the test meal were lactulose 23.4 ppm, bread 15.2 ppm at 3 and 7 hours respectively. Initial mean colonic pH values did not significantly differ between studies (mean $\pm$s.d.)(6.42 $\pm$0.67, 6.35 $\pm$0.78, 6.13 $\pm$0.60). Colonic pH dropped over time following all meals but only bread produced a drop significantly different to the other meals. A minimum mean pH of 4.85 was found at 5 hours after the bread meal, compared to 5.70 $\pm$0.80, and 6.43 $\pm$0.42 for the control and lactulose meals respectively at the same time. No significant correlation was found between breath hydrogen production and colonic pH.

Conclusions: The complex polysaccharides in bread ferment more slowly than the soluble disaccharide lactulose, and lower colonic pH to a greater extent. This supports the view that different sources of fibre have varying effects on the colonic environment.

W79

EFFECT OF FISH OIL ON RECTAL ALPHA- TOCOPHEROL STATUS IN PATIENTS AT HIGH RISK FOR COLON CANCER.

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Potentially beneficial effects of fish oil (F.O.) have been reported in patients with active Inflammatory Bowel Disease and recently omega-3 polyunsatured fatty acids (omega-3 FA) were shown to induce kinetic changes in the rectal mucosa of patients at high risk for colon cancer (M.Anti, Gastroenterology,1991;100:A347). The incorporation of omega-3 FA in cell membranes make them more unsatured and potentially more unstable and it has been suggested that some biological effect of F.O. is mediated by an enhancement of lipid peroxidation. Vit. E is a potent antioxidant agent and its content in body tissues is known to be largely related to the cell lipid composition. In this study we assessed the effect of omega-3 supplementation on the rectal alpha-tocopherol status in patients with sporadic colonic adenomas. PATIENTS AND METHODS: 15 patients with sporadic colonic polyps, fed a strictly controlled mediterranean diet, were supplemented for 4 weeks by 1.36 g/die of eicosapentaenoic acid (EPA) and 1.2 g/die of docosahexaenoic acid (DHA). Fatty acid composition (Gas cromatography) and vit. E concentration (HPLC) were assessed in plasma, red cell membranes and rectal mucosa (endoscopic biopsies) before the supplementation (time 0) and at 2 and 4 weeks. In addition malonaldehyde (MDA) plasma levels were assayed (TBA at 535 nm) as a marker of lipid peroxidation. Rank test was used for statistical analysis. RESULTS: The fatty acid pattern equally changed in red cell membranes and rectal mucosa during the supplementation (EPA and DHA increased; arachidonic acid decreased). Plasma levels and the content of Vit E in red cell membranes and in biopsy samples are reported in the table.

	Time 0	2 wks	4 wks
- Plasma (μM/ml)	19.4±1.9	19.5±2.0	25.8±2.6*
- Red cells (ng/mg)	224±16	276±19*	269±24*
- Rectal mucosa (ng/mg)	103±16	161±40	57.9±8.7*

* P<0.05 vs time 0

MDA plasma concentrations progressively increased during F.O. intake. CONCLUSIONS: As expected lipid peroxidation is potentiated by changes of cell membranes fatty acid composition. Vit.E is consumed in the rectal mucosa during a supplementation with F.O. probably as a consequence of a forced activity of scavenging against oxigen derived free radicals. This event should be taken into consideration when designing and interpreting experiments in which biological or clinical effects of fish oil are evaluated.

W80

EXPRESSION OF E-CADHERIN ADHESION MOLECULES IN COLORECTAL CANCER.

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During the process of tumorigenesis profound alterations take place in intercellular and cell to stroma interactions. Cadherins are transmembranous Ca^{++}-dependent cell-cell adhesion molecules involved in various processes of intercellular adhesion. The different members of the family include N-Cadherin (present mostly in neural tissue), P-Cadherin (present mainly in the placenta and non epithelial cells)and E-Cadherin (expressed in epithelial tissues).

Using immunocytochemical methods we analysed 65 colorectal carcinomas, 18 adenomas and non neoplastic colonic mucosa from the above cases with a monoclonal antibody (6F9) to E-Cadherin.

Positive labelling was obtained in 16 of the 18 adenomas and in 37 of the 65 carcinomas. Normal colonic mucosa was also positively labelled. None of the 8 poorly differentiated tumours was stained with 6F9 but loss of expression was also detected in 12 out of 31 well differentiated tumours. There was no statistically significant correlation between the expression of E-cadherin and Dukes' classification.

Our result indicate that during colorectal tumorigenesis some tumour cells show impaired E-cadherin related intercellular adhesion, which may have implications for local tumour spread and metastasis.

W81

INTERPHASE NUCLEOLAR ORGANIZER REGION (AgNOR) AND CELL REPLICATION IN COLORECTAL CANCER.

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AgNOR count has been proposed as a useful parameter for evaluating cell replication in various human tumours. The technique is relatively easy and can be carried out in paraffin embedded sections. It is not known, however, how AgNORs compare with the more traditional parameters of cell proliferation. In 40 patients with colorectal cancer we purposed therefore to compare AgNOR count with Labelling Index (L.I., fraction of S-phase cells) evaluated either with in vivo administration of Bromodeoxyuridine (BdUr) or after incubation of small fragments of neoplastic tissue with 3-H-Thymidine. The patients were given BdUr (500 mg) 4-6 hours before surgery and S-phase cells were identified with standard immunohistochemistry (BdUr) or autoradiography (3-H-Thymidine). No correlation was found between AgNOR number and either BdUr L.I. ($r=0.32$, n.s.) or 3-H-Thymidine L.I. ($r=0.3$, n.s.). In contrast, BdUr and 3-H-Thymidine L.I.s were significantly correlated ($r=0.6$, $p<0.02$). AgNOR count was unrelated to the age of patients, sex, site and diameter of tumours, pattern of growth, grading, staging and density of microvessels (evaluated with anti Factor VIII antibodies). In conclusion, AgNOR number does not seem to be related to the more direct parameters of cell kinetics; it follows that its value as a biomarker of cell proliferation remains questionable, at least in colorectal neoplasms.

W82

CANCER OCCURRENCE IN THE FOLLOW-UP OF 25 FAMILIES WITH HEREDITARY NON-POLYPOSIS COLORECTAL CANCER (HNPCC).

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HNPCC is an autosomal dominant disorder featured by susceptibility to intestinal cancer, usually at early onset and localized in the right colon. Several other tumours (Endometrium, Skin, Stomach, Ureter, Biliary Tract) may occur with increased frequency in these families. Between 1983 and 1989, 25 families with HNPCC were identified in our Health Care District; aim of this study is to describe the occurrence of cancer in the 6.2 years average follow-up (range 2-9) of these families, by comparing the observed number of cancers with the expected number based on incidence rate, by site, from a Cancer Registry. The 625 family members at risk contributed to 2,730 person-years of observation. Thirty-four cancers of various sites developed in the follow-up versus 22.1 expected (Odds Ratio, OR, 1.41, Confidence Intervals, CI, 1.16-1.79, P=0.05). However, the excess was consistently higher in the age-groups 41-50 (observed 10, expected 1.8, OR 6.6, CI 3.7-11.6, P<0.001) and 51-60, whereas was no more evident in older individuals. Nineteen out of 34 cancers were localized in the colon-rectum (expected 3, OR 6.8, CI 4.2-9.4, P<0.001). Again, this excess was more marked in age groups 41-50 and 51-60, but remained elevated in the older groups. No other tumour showed an increased occurrence during the follow-up. In Conclusion, the results show an increased overall occurrence of cancer among families with HNPCC of borderline significance. In contrast, members of these families continue to be at a highly significant risk of colorectal cancer at all ages and in a relatively short period of observation.

W83

MUCOSAL PROLIFERATION, COLORECTAL CANCER RISK AND VEGETARIANS

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Vegetarians have low rates of colorectal cancer (CRC). There have been limited studies of rectal mucosal proliferation amongst vegetarians of long standing.

We studied rectal mucosal proliferation in 15 long standing (>10 years) vegetarians with no family or personal history of CRC. We compared this group to a group of known low risk (normal colonoscopy and no family history of CRC) n=21 taking a mixed diet, and to two known high risk groups those with adenomas n=42 and those with a strong family history of CRC n=23.

Mucosal proliferation was measured on rectal biopsies using the in vitro metaphase arrest technique Crypt Cell Production Rate (CCPR).

Results:

	Median CCPR cc\c\hr	Mann Whitney Z=	Significance p=
Vegetarians n=15	10 (2-17)	-	-
Low risk n=21	10 (4-24)	0.03	0.9
Adenoma n=42	13 (6-25)	2.48	0.01
Family history n=23	13 (6-29)	2.56	0.01

Vegetarians have similar proliferation indices to those in an established low risk group and significantly lower proliferation than individuals of high risk.

Low proliferation amongst vegetarians may explain low rates of CRC in this group.

W84

RELATIONSHIP BETWEEN TUMOUR GRADE, VASCULAR PATTERNS AND MODE OF PRESENTATION IN COLORECTAL CARCINOMA.

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The vascularity of 10 moderately differentiated and 9 poorly differentiated human colorectal carcinomas was studied using the QB/end/10 monoclonal antibody to demonstrate blood vessels immunohistochemically. It was found that the presence of grossly distended blood vessels near the luminal surface was a prominent feature in all of the moderately differentiated tumours, whereas such vessels were consistently absent in the poorly differentiated cancers. Because this was felt to have potential implications of haemorrhage into the gut lumen, the mode of presentation of each tumour was established. Of the 10 moderately differentiated tumours, 9 presented with frank rectal bleeding or clinical anaemia compared with only 2 out of the 9 poorly differentiated tumours (chi^2 with Yate's correction = 6.36, $p<0.01$). In addition, the haemoglobin level was below the normal range in 8 out of the 10 patients with moderately differentiated tumours compared with 2 out of the 9 patients with poorly differentiated tumours (chi^2 = 4.24, $p<0.05$). These findings suggest that poorly differentiated tumours may bleed less than moderately differentiated tumours owing to differences in patterns of vascularity. This may have important implications of the interpretation of symptoms and faecal occult blood testing.

W85

THE PASSAGE OF FLATUS IN NORMAL AND CONSTIPATED SUBJECTS.

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Patients with Slow Transit Constipation (STC) are said to have defective colonic propulsion. Those with Obstructed Defaecation (OD) have a sphincter defect. We have used an analogue system of ambulatory anorectal monitoring of anal and rectal pressures to determine the physiology of the passage of flatus in both groups and in normal subjects (N).
Recordings from 11 normal subjects age 36 years (range 25-74), 15 with STC age 35 (18-64) and 10 with OD age 38 (24-72) were analysed.
Actual passage of flatus is similar in all groups (N= 2 events per recording [range 0-6] : STC = 1 [0-5] : OD = 2.5 [0-5]), except the anorectal gradient favouring flatus is greater ($p<0.05$) in STC (N = median anal to rectal pressure gradient -52.5 cmH2O {-145 to 0} : STC = -65 {-150 to -10} : OD = -32.5 {-95 to -10}).
However, taking an overview of all the patients, 3 distinctive styles of passing flatus are discernible : type 1 - a drop in anal pressure (-55 cmH2O {range -100 to -20}) and a rise in rectal pressure (+90 {25 - 165}) : type 2 - a drop in anal pressure (-80 {-90 to 40}) but unchanged rectal pressure : and type 3 - a rise in anal pressure (+45 {+10 to +105}) and a greater rise in rectal pressure (+145 {+110 to +190}) facilitating passage of flatus.

W87

MEDIUM CHAIN TRIGLYCERIDES IN EXOCRINE PANCREATIC INSUFFICIENCY: EVALUATION OF ABSORPTION BY CHEMICAL METHODS

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Medium chain triglycerides (MCT) are considered to be better absorbed than long chain triglycerides (LCT) in exocrine pancreatic insufficiency.

Since the Van de Kamer method for fecal fat assay does not extract completely MCT from feces, the reported decrease in steatorrhea after MCT administration could be simply due to an analytical underaestimation. Aim of this study was to compare the absorption of MCT and LCT in pancreatic insufficiency by measuring fecal fats both by the Van de Kamer and by the Jeejeebhoy (Clin Biochem 1970; 3:157) method, which measures MCT as efficently as LCT. We studied 4 patients with pancreatic insufficiency (Pancreolauryl test TK <10%; fecal fats > 20 g/day) due to chronic pancreatitis (1) or to protein-caloric malnutrition (3); all were on a diet containing 60 g of fats. For 5 days, 30 g of LCT (period A), 30 g of MCT (period B) or 30 g of MCT and pancreatin (150000 IU of lipase/day) (period C) were added to this diet. In the last 3 days of each period, feces were collected, weighted and assayed for fecal fat. Steatorrhea (g/day, x±SE) and the significance of the difference between the periods (co-variance analysis) are reported in the table:

	period A	period B	period C	
- Van de Kamer	22.2±7.0	17.6±6.6	10.6±2.4	NS
- Jeejeebhoy	51.3±13.5	31.9±11.4	17.8±5.2	p=.05

A good correlation was found between the two methods ($y=0.1+0.54x$, $r=0.938$), even if the Van de Kamer method gave much lower results then the other; a similar difference between the two methods was found in periods with or without MCT in diet.

In conclusion, lower results are obtained by the Van de Kamer than by the Jeejeeebhoy method; in pancreatic insufficiency, MCT are absorbed better than LCT; fecal fat losses are reduced by the pancreatic extracts, even when MCT are added to the diet.

Pancreas W86–W94

W86

OMEPRAZOLE IMPROVES FAT ABSORPTION IN CYSTIC FIBROSIS.

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Gastric acid hypersecretion is one of the major factors contributing to the continuing problem of fat malabsorption experienced by some patients with cystic fibrosis (CF). Despite supraphysiological doses of pancreatic enzyme supplements, the consequent acidic duodenal environment in the postprandial period causes progressive and irreversible inactivation of lipase. Omeprazole, by effecting a complete block of gastric acid secretion will increase the postprandial duodenal pH and thus produce a more favourable environment for enzyme action. We are thus undertaking a study to assess the effect of omeprazole administration on duodenal pH and fat absorption in children with CF.

Five children (age 6months-12years) attending the sub-regional CF clinic at Sheffield Childrens' Hospital were enrolled into a 3 month trial of omeprazole therapy (dosage; 10mg od age <3years: 20mg od age >3years). 24 hour ambulatory gastric and duodenal pH monitoring (dual channel antimony electrode, Synectics Medical), fat absorption following a standard fat meal and liver function tests were measured before and after treatment. The children were seen monthly in clinic and anthropometry performed by a single trained technician.

Weight gain improved in all children. There was no significant change in postprandial duodenal pH (% time pH<5), however, triglyceride rise following the standard fat meal increased significantly ($p=0.05$). There was no change in liver function tests. Gastrin levels are awaited. The drug was well tolerated with no adverse events.

This study suggests that omeprazole may have a useful role in the promotion of fat absorption in patients with CF despite the incomplete acid block. Further work is required to establish the dosage requirements, which would seem to be high in these children, and to assess whether a more significant reduction in gastric acid secretion would further promote fat absorption.

W88

SYMPTOM RELIEF AFTER STENTING FOR MALIGNANT BILE DUCT OBSTRUCTION.

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The insertion of a biliary stent is accepted treatment for relief of jaundice and itching in patients with cancer of the head of the pancreas. Many patients also complain of anorexia and indigestion (heartburn, bloating and wind), but there have been no attempts to assess the effect of stenting on these latter two symptoms. The aim of this study was to assess the effect of stenting on all symptoms. 10 patients have completed a standard questionnaire pre stent and at intervals post stenting for up to 3 months. Individual symptoms were scored on a scale of 0-3, 0=no symptoms, 1=mild, 2=moderate, 3=severe. At the 4 week assessment which all patients have completed, each patient had complete relief of jaundice (mean score pre stent 2.6, post stent 0) and itching (pre 1.3, post 0). In addition there was a marked improvement in symptoms other than jaundice and itching. 8 patients had moderate/severe (grade 2/3) anorexia before stent insertion and in 3 this was their most distressing symptom. In all of these patients stenting has improved appetite and in 5 anorexia has been completely relieved (grade 0). 7 patients had moderate/severe indigestion before stent insertion. In 6 this has improved after the procedure with complete relief in 3.

	Pre-stent mean symptom	Post-stent score	P value Wilcoxon signed rank test
Anorexia	2.3	0.4	0.01
Indigestion	2.0	0.6	0.01

In conclusion, stent insertion is a very effective treatment for the anorexia and indigestion associated with cancer of the head of the pancreas and significantly improves quality of life. Furthermore this finding will provide a basis for further study to understand this particular form of cancer associated anorexia.

W89

THE ISLET-ACINAR AXIS - A ROLE FOR GLUCAGON ?

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It is unknown, whether glucagon plays a role in the regulation of the exocrine pancreas via the islet-acinar axis. Therefore we investigated the effect of endogenous glucagon on exocrine pancreatic secretion.

The isolated perfused rat pancreas was used. The exocrine pancreas was stimulated half maximally by CCK-8 (15 pMol/L). Glucagon release was stimulated by a low glucose concentration (1.8 mMol/L) and arginine (20 mMol/L). In further experiments either glucagon antibodies (TR 211, final dilution 1: 520) or cysteamine (10 mMol/L) were added to the perfusate. Amylase activity in pancreatic juice and hormone concentrations in the effluent were measured. (n= 8; $p<0.05$).

Arginine stimulated glucagon release (23.2±1.7 vs. 0.3±0.02 ng/20 min) and inhibited CCK-stimulated amylase secretion (4.0±0.3 vs. 14.3±0.9 U/min). Infusion of glucagon antibodies immunoneutralized arginine-induced glucagon release and reversed inhibition of amylase release (12.8±1.2 vs. 4.0±0.3 U/min). Cysteamine released somatostatin (212±28 vs. 79±8 fmol/20 min), inhibited glucagon secretion (11.3±0.8 vs. 21.1±1.6 ng/20 min) and reversed arginine-induced inhibition of amylase release (14.2±1.7 vs. 7.0±0.5 U/min).

We conclude that endogenous glucagon or glucagon-like peptides play a role in the regulation of the acinar cell. Within the concept of the islet-acinar axis insulin and glucagon seem to have opposing effects on exocrine pancreatic secretion.

W90

EVIDENCE FOR AUTOCRINE LOOPS INVOLVING FIBROBLAST GROWTH FACTORS (FGFs) AND THEIR RECEPTORS (FGFRs) IN HUMAN PANCREATIC ADENOCARCINOMA.

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The structure and expression of the seven human FGFs and four FGFRs are examined in a panel of 14 human pancreatic cancer cell lines using specific cDNA probes. There is evidence of differential expression of individual FGFs and FGFRs forming potential autocrine loops in 6 out of 14 cell lines (>40%). A further 5 cell lines (i.e. 35%) express mRNA for FGFRs in the absence of FGF synthesis, hence forming potential targets for paracrine action.

We are currently extending this study in surgical specimens from resected human tumour tissues.

W91

EXPRESSION OF GLUTATHIONE S-TRANSFERASES IN NORMAL AND MALIGNANT PANCREAS.

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The glutathione S-transferases (GST's) are a family of isoenzymes that detoxify xenobiotics and cytotoxic drugs and so have been implicated in both the suseptability to enviromental carcinogens and resistance to chemotherapy. Point mutations have recently been found in K-*ras* oncogene in a high proportion of pancreatic tumours, implicating enviromental carcinogens in pathogenesis and clinically the tumour is characterised by marked chemotherapeutic drug resistance.

The aim of this study was to assess the distribution of the 3 cytosolic GST's acidic (pi), basic (alpha) and neutral (mu) in adult pancreas compared to ductal adenocarcinoma.

Method. 5µm formalin-fixed paraffin-embedded material of normal pancreas (n=5) and pancreatic ductal adenocarcinoma (n=26) were examined. Sections were incubated with the primary polyclonal antibodies acidic GST (1/400), basic GST (1/500) and neutral GST (1/200) at 4°C overnight. Immunostaining was carried out using an indirect immunoperoxidase method with 3,3' diaminobenzidine as the chromagen.

Results.(1)Normal Pancreas. The large ducts stained strongly with both acidic and basic GST. However the intralobular ducts and centroacinar cells only showed immunoreactivity with acidic GST whereas exocrine acinar cells expressed only basic GST. No immunoreactivity was seen with neutral GST in the exocrine pancreas but the islets of Langerhans stained weakly. (2)Ductal adenocarcinoma. 16/26 (61%) cases showed strong immunoreactivity for acidic GST which was cytoplasmic and heterogenous.This contrasted with weak focal staining for basic GST in 4/26 (15%) of cases. As in normal pancreas no immunoreactivity was seen with neutral GST.

Summary. The presence of predominantly acidic GST in pancreatic carcinoma is in agreement with that seen in other tumours and may reflect induction of acidic GST resulting in tumour drug resistance. Alternatively the pattern of isoenzyme distribution may reflect cell phenotype , so suggesting the centroacinar cells and/or intralobular ducts rather than the large ducts as the cell of origin of pancreatic ductal adenocarcinoma.

W92

DYNAMIC DIETHYL HIDA (D-HIDA) IMAGING IS USEFUL IN THE INVESTIGATION OF CHRONIC UPPER ABDOMINAL PAIN

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The role of dynamic D-HIDA imaging in the investigation of recurrent upper abdominal pain was studied in 42 patients. All subjects had recurrent pain for 18 (8-150) months)* and had not improved after antacid therapy. Their ages were 45 (24-76) years*. There were 30 females and all had previously undergone normal abdominal ultrasound and upper GI endoscopy examinations.

Dynamic D-HIDA imaging was performed after cholecystokinin (CCK) infusion and the following parameters measured: 1) Latent period before gallbladder emptying (LP); 2) Ejection period (EP); 3) Ejection fraction (EF); and 4) Ejection Rate (ER). An abnormal result was defined where the EF was outside the range 35%-50%.

	LP	EP	EF	ER
Normal results (n=7) (EF 35%-50%)	11.5 (1-16)*	21.0 (10-25)*	38.0 (36-42)*	1.5 (1.4-1.8)*
Abnormal Results (n = 35)				
1) Low EF (n=23) (35%)	9.5 (2-14.5)*	14.5 (7-18)*	18.2 (7.4-30.3)*	1.2 (0.5-4.2)*
2) High EF (n=12) (50%)	4.0 (0-10)*	13.0 (7-20)*	74.0 (51.3-82)*	4.2 (3.6-8.0)*

Twenty-seven patients underwent cholecystectomy because of persistent biliary pain (4 from normal group, 23 from abnormal group) and 25 of these patients are symptom free on follow-up. All gallbladders removed showed chronic cholecystitis. Ten of the 15 patients who did not undergo surgery have persistent pain.

These data show that dynamic D-HIDA imaging after CCK stimulation may have an adjunctive role in identifying those patients with persistent biliary-type pain who would benefit from cholecystectomy.

* = median (range)

Liver W95–W105

W93

A NEW METHOD FOR MONITORING INTRACELLULAR PH (pHi) IN ISOLATED RAT PANCREAS USING CONFOCAL LASER SCANNING MICROSCOPY

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A new model was developed for investigation of pHi-regulation of isolated rat pancreas. Using confocal laser scanning microscope technique the different pancreatic cell types could be studied in their functional arrangement under minimal destruction of the organ integrity.

According to the method of Kanno celiac artery was cannulated and the splenic pancreas segment was perfused with a dextran (5%)-Ringer solution at a constant flow rate of 2 ml/min. Cells were loaded with a pH-sensitive fluorescent dye (BCECF) by topical application of 10µmol/l of the membrane-permeant ester BCECF-AM for 15-30 min. After fixation of pancreas in a temperature-controlled (37°C) plastic chamber, pH measurements were performed with a Biorad MRC-600 confocal microscope. Two lasers, Ar and HeCd, served for specimen illumination at the pH-sensitive (490 nm) and pH-insensitive (440 nm) line of BCECF. After each experiment dye calibration was done extracellularly in small glass capillaries filled with medium and dye comparable to intracellular conditions at defined pH-values.

Image analysis enabled the detection and comparison of different cell types. Preliminary results showed no difference in pHi of acinar cells and endothelial cells. pHi in both cell types decreased after a CO_2-pulse and recovered after CO_2 wash-out. Na-free solution potentiated this effect suggesting the involvement of a Na^+/H^+ exchanger. This new experimental system should provide further insight into intracellular pHi-regulation of different pancreatic cell types (e.g., acinar, ductal and endothelial cells).

The main advantage of this approach is the observation of pancreatic function under conditions of preserved tissue structure and cellular architecture. This may be of specific value, for example, in the investigation of pathogenesis of experimentally induced acute pancreatitis.

W94

CHOLECYSTOKININ (CCK) IN THE REGULATION OF INSULIN, GLUCAGON AND PANCREATIC POLYPEPTIDE (PP) RELEASE IN MEN.

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CCK is an example of a gut peptide hormone with an established insulin-releasing effect, but the role of endogenous CCK in the physiological control of endocrine pancreas has not been elucidated definitely. This study was designed to determine the involvement of CCK released postprandially in the secretion of insulin, glucagon and PP using loxiglumide, a highly specific antagonist of type A CCK receptors.

Basal and postprandial plasma concentrations of insulin, glucagon and PP were measured by specific RIAs in 8 healthy volunteers given 500ml of a standard mixed meal (Fresubin®, Fresenius, Bad Homburg, Germany) consisting of protein (4.4%), fat (3.4%) and carbohydrates (14%), 1kcal/ml, at breakfast, lunch and supper time. Placebo or loxiglumide (1200mg p.o.) was administered 30 min before each meal, and blood samples were taken at 60 and 30 min before and 30, 60 and 90 min after each meal.

In placebo treated subjects, plasma CCK rose from basal of 1.2±0.4 to peak values of 5.1±0.6 pM/l after meal (Scand.J.Gastroenterol.25:731,1990). The respective postprandial increase in plasma insulin was from 10±2 to 53±6 uU/ml, in plasma glucagon from 47±6 to 76±11 pM/l and plasma PP from 24±3 to 70±9 pM/l. Loxiglumide did not affect significantly the postprandial increments in plasma insulin and glucagon levels, but reduced significantly increment in plasma PP.

This study provides some evidence that endogenous CCK plays little role in the postprandial insulin or glucagon secretion, but significantly affects the release of PP via the type A of CCK receptors.

W95

EPIDEMIOLOGY OF HCV INFECTION IN BLOOD DONORS

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In the first six months of testing for anti-HCV, the South Western Regional Transfusion Centre has screened 89,454 donations, using the UBI Elisa.

Sixty (0.06%) were confirmed positive and 36 (0.04%) indeterminate by RIBA-2 testing. All these cases were invited for a counselling interview. To date 54 donors have attended (39 positive, 15 indeterminate). Six of the RIBA-2 indeterminate donors were C22 positive only. All have completed a confidential medical and epidemiological questionnaire. Thirty-eight (70%) were males. Thirty were aged between 33-42 years.

Twenty-three (43%) of the donors (22 positive, 1 indeterminate) had injected drugs in the past. Of these, none admitted to use in the last 5 years, and 8/23 were exposed more than 15 years ago. Nineteen (82%) had shared needles.

Other risk factors elicited included tattooing in 15 (28%) and ear-piercing in 34 (66%). Eleven donors (20%) had had a blood transfusion, but none of these had a previous history of jaundice or hepatitis. Four donors had had electrolysis or acupuncture. Fifteen (28%) have worked in health care.

Five of the 34 positive donors had no apparent risk factors and may therefore represent sporadic disease.

This data raises the possibility of a cohort of cases born in the 1950s who have abused drugs in their late teens and early twenties and appear to be at increased risk of HCV infection. If this is confirmed by prospective studies in the community, there will be implications for the future provision of health care for this group.

W96

A LASER DOPPLER STUDY OF GASTRIC BLOOD FLOW IN PORTAL HYPERTENSION

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There is conflicting evidence on the effect of portal hypertension (PHT) on gastric mucosal blood flow. Using endoscopic laser Doppler flowmetry, we measured regional gastric perfusion in 28 PHT patients with a history of bleeding oesophageal varices who were on a programme of maintenance sclerotherapy. We also studied 19 control patients with no evidence of liver disease or PHT. Measurements were performed on the greater and lesser curves at proximal, middle and distal levels of the stomach.

Results (arbitrary perfusion units, averaged over greater and lesser curves, expressed as median and interquartile range):

Level	PHT	Control
Proximal	183 (144-240)	200 (173-238)
Middle	143 (113-188) *	215 (143-270)
Distal	114 (99-150) *	148 (120-180)

* $p<0.05$ relative to control.

In both PHT and control patients, there was a significant decreasing flow gradient from proximal to distal stomach ($p<0.01$), but no significant difference between greater and lesser curves. Perfusion was significantly lower in PHT than control patients in the middle and distal stomach. Within the PHT group, there was no significant relationship between blood flow and the presence of congestive gastropathy, the size of oesophageal varices, or the number and timing of previous sclerotherapy sessions.

Conclusion: gastric blood flow is reduced in PHT patients on maintenance sclerotherapy.

W97

PERCENTAGE HEPATIC REPLACEMENT AND THE GROWTH RATE OF COLORECTAL LIVER METASTASES

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Percentage hepatic replacement (PHR) can quantify the extent of hepatic metastases (CRHM) however it is unclear whether a process of hepatic replacement accurately describes the natural growth of tumour within normal hepatic parenchyma.

We have studied the PHR growth of untreated CRHM (n=32) and hepatic parenchymal volumes (n= 11) using the technique of planimetry applied to computerised tomographic images of the liver. PHR was used as a measure of tumour volume to minimise extrahepatic effects on tumour growth. To compare growth of metastases with variable PHRs, natural logarithmic changes of PHR were employed (LPHR/100days)

The median PHR of metastases studied was 0.49% (range 0.09 - 18.2%) subsequent assessment 72 days later (median, range 14 - 235 days) showed a significant increases in PHR to 1.78% (median, range 0.1 - 22.9%)(paired t $P < 0.001$). The LPHR/100days of metastases with PHR > 5% was 0.18 (median, IQR 0.13-0.32). Growth of metastases with PHR < 5% was significantly greater (LPHR/100days 1.1 median, IQR 0.77 - 1.47. $P < 0.01$ Mann Whitney U test).

Non neoplastic hepatic parenchymal volumes (1819 cc median, IQR 1647 - 1997cc) was shown to increase (2200 cc median, IQR 1590 - 2401 cc) ($P = 0.005$ paired t) as metastatic burden increased.

These findings demonstrate that the growth rate of hepatic metastases is greatest when metastases are small. As metastases grow larger within the liver, normal non neoplastic hepatic parenchymal volume also enlarges. This suggests that growth of CRHM within livers is more complicated than a simple process explained as hepatic replacement.

W98

Identification of four families with hereditary haemochromatosis showing discordance between HLA Class I gene and the disease locus.

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First degree relatives of 4 probands with hereditary haemochromatosis were screened for haemochromatosis by estimating serum iron, ferritin and % transferrin saturation along with HLA typing for A and B antigen. In all the families the parents of the proband were not available for screening. In two families the proband had only two siblings and due to this small size of the family the HLA haplotypes of the parents could not be deduced. In the first family 2 siblings HLA identical to the proband have no evidence of iron overload. In the second family again 2 siblings were HLA identical to the proband. One of them has haemochromatosis while the other who is now 30 years old has over the past 5 years shown no evidence of iron accumulation. Seven siblings of the third proband were screened and all the 4 HLA haplotypes contributed by the parents could be deduced. Of the 2 HLA identical siblings only one has haemochromatosis while the other who is in his 60's has no iron overload. Six siblings of the fourth proband (HLA A3 B7, A3 B14) were screened and 2 sisters were found to be HLA identical to him. Only one of them has iron overload while the other (60 years old) who has been followed up over the last 6 years has as yet no evidence of iron overload. A brother(HLA A3 B7, A3 B8)inspite of having recombination between HLA A and B locus has haemochromatosis.

We have identified 4 families with haemochromatosis where there is discordance between HLA Class I gene and the disease locus. In two families the discordance appears to be due to recombination. One member with recombination between HLA A and B locus retaining haemochromatosis gene has also been identified.

W99

A FOUR COMPARTMENT MODEL TO DETERMINE BODY COMPOSITION IN LIVER CIRRHOSIS.

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In order to identify body compartment abnormalities in patients with cirrhosis, we have developed a method of measuring the main body components. Dual energy X-ray absorptiometry (DEXA) was used to determine fat-free mass (FFM) and total body fat (TBF). Total body potassium (TBK) to determine body cell mass (BCM), and the extracellular solids (ECS) component of FFM was derived from the total body bone mineral content obtained from DEXA. This enabled extracellular water (ECW) to be estimated by subtraction of BCM and ECS from FFM.

Body composition was determined in a group of 52 patients with established cirrhosis, consisting of 22 (M:F/11:11) patients with fluid retention and 30 (M:F/8:22) patients with no evidence of fluid retention. They were compared to a control group of 54 normal subjects (M:F/28:26) who were of similar age, height and weight. FFM and TBF derived from DEXA showed no significant differences between control and patient groups. However BCM (expressed as a percentage of FFM) was significantly reduced in both male patient groups compared to controls; with fluid retention (mean difference = -11.2%, $P<0.001$), without fluid retention (-8.1%, $P<0.005$). Only female patients with fluid retention showed reduced BCM (-5.3%, $P<0.01$). ECW was significantly increased in both male patient groups compared to controls: with fluid retention (+6.2Kg, $P<0.001$), without fluid retention (+4.1Kg, $P<0.005$). The female patients with fluid retention also had significantly increased ECW compared to controls (+2.2Kg, $P<0.05$).

In Summary, this four compartment model demonstrates the loss of BCM and accumulation of ECW that occurs in cirrhosis, and is of potential use for investigation of body composition changes in relation to disease severity and duration.

W100

EVIDENCE FOR LIPID PEROXIDATION IN RATS CHRONICALLY FED ALCOHOL

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Chronic alcohol consumption induces a second enzyme system, cytochrome P_{450} 11E1, that enables habitual abusers to consume far greater quantities of alcohol than normal. This pathway of metabolism may lead to the production of free radical species, which may cause tissue damage by peroxidation of cell membranes.

Groups of Wistar rats of equal male:female ratio (n=30), were fed alcohol by gavage twice daily to achieve a dosage of 15 mg/kg body-weight. Peak blood alcohol concentrations of greater than 250mg% were produced. The animals were allowed ad libitum access to standard laboratory chow and water. Control animals were pair-fed to the alcoholic group, and fed isocaloric glucose by gavage.

Groups of animals were sacrificed at between 9-10 am on consecutive mornings, after nocturnal feeding, since we have previously shown that fasting rapidly depletes hepatic glutatione levels. Hepatic glutathione was measured by a spectrophotometric enzymatic recycling procedure. As a marker of lipid peroxidation, hepatic malonaldehyde (MDA) was measured by high performance liquid chromatography.

Hepatic MDA was greatly increased in the alcoholic group ($p<0.0001$), as was hepatic total glutathione ($p<0.001$).

The increased MDA production in the alcoholic group is strong evidence that lipid peroxidation is a mechanism of alcoholic tissue damage. The rise in hepatic glutathione may be an adaptive response to free radical production that protects the rat against tissue damage.

W101

HOW USEFUL IS SKINFOLD ANTHROPOMETRY IN LIVER CIRRHOSIS? A COMPARISON OF TECHNIQUES TO MEASURE BODY FAT MASS.

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The measurement of body composition in liver disease is beset with difficulties. We compared Dual Energy X-ray Absorptiometry (DEXA) which provides an accurate and direct estimation of total body fat (TBF_{DEXA}), to three indirect methods of determining total body fat (TBF): Skinfold anthropometry (TBF_{SFA}), Bio-electrical impedance (TBF_{BIA}) and Total body potassium (TBF_{TBK}). 20 males and 33 females with histologically proven cirrhosis of various aetiologies were studied, of whom 23 had fluid retention.

For all patients (n=53), TBF_{DEXA} (mean+SD 19.2±8.2Kg) showed significant correlations (all P<0.00001), with TBF_{SFA} (17.2±6.2; r=0.93), TBF_{BIA} (19.8±9.9;r=0.78) and TBF_{TBK} (21.9±8.4; r=0.77). However, there were significant differences (all P<0.001) between TBF_{DEXA} and TBF_{SFA} (Bias=+2.0Kg, 95%CI 1.1 to 2.9Kg) and TBF_{TBK} (Bias= -2.7Kg,95%CI -4.2 to -1.2Kg). Only TBF_{BIA} showed no significant bias. When the male and female patients were examined separately, a similar pattern of bias and correlations were noted between DEXA and the other indirect methods. In the presence of fluid retention in the males (N=12; TBF_{DEXA} (13.9±6.2Kg) there was close correlation with TBF_{SFA} (13.2±6.8Kg;r=0.94, P<0.00001) with insignificant bias, TBF_{BIA} (15.8+7.7Kg;r=0.45; P>0.1) showed no correlation and TBF_{TBK} showed significant correlation but with a large bias (22.2±8.4Kg;r=0.72,P<0.01; Bias= -8.3Kg, P<0.001). When female patients with fluid retention were considered, TBF_{SFA} showed the closest correlation to TBF_{DEXA} with no bias (r=0.93; P<0.0001).

In summary, skinfold thickness estimations appear to represent the most accurate and easily performed of the indirect methods of TBF estimation, with close agreement to DEXA even in the presence of fluid retention.

W102

DOES FOREARM BONE MINERAL DENSITY ACCURATELY REFLECT LUMBAR AND FEMORAL NECK OSTEOPENIA IN LIVER CIRRHOSIS?

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It is well recognised that patients with cirrhosis are at risk of developing osteopenia. Single photon absorptiometry (SPA) of the forearm has been used extensively to quantify changes in bone mineral density (BMD), but now dual energy X-ray Absorptiometry (DEXA) allows accurate determination of BMD in the regions of particular clinical interest, lumbar spine (L2-4) and femoral neck. We undertook a survey of 68 female patients to determine if forearm BMD reflects bone loss that occurs in the axial skeleton.

Three groups of patients were examined, 24 cholestatic cirrhosis (CHOL, mean age 55 yrs, Child-Pugh score(CPS) =7.5), 26 non-cholestatic cirrhosis (NCHOL, age 50 yrs, CPS=7.8), and 18 post liver transplantation (OLT, age 51yrs, mean time since OLT = 7.5 months). 41 controls (CON, age 51yrs) were observed concurrently to determine the normal correlations between forearm, spine and femoral neck BMD. A local population of 329 females were studied to provide normal ranges for DEXA, and a separate group of 249 females provided norms for SPA. BMD difference from the local populations was expressed as Z scores.
No relationships were found between degree of osteopenia at any site and severity or duration of liver disease. CON forearm Z scores showed correlations with spine (n=41, r=0.45, P<0.005), and femoral neck (r=0.50, P<0.001). CHOL had a reduction in spinal BMD (mean Z score -0.86, 95%CI -1.34 to -0.37, P<0.002) and forearm (-1.01, 95%CI -1.54 to -0.49, P<0.001). CHOL forearm Z scores were correlated with spine (n=24, r=0.71, P<0.0001), and femoral neck (r=0.48, P<0.02). The NCHOL BMD Z scores were not reduced, with no correlation found between forearm and axial BMD. OLT BMD Z scores were significantly reduced at each site (all P<0.01), with no correlation found between forearm and axial bone loss.

In summary, in female patients, measurement of forearm BMD was only of use in predicting axial BMD loss in patients with cholestatic cirrhosis.

W103

LEFT VENTRICULAR FUNCTION IN RESPONSE TO EXERCISE IN PATIENTS WITH ALCOHOLIC AND NON ALCOHOLIC CIRRHOSIS

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Alcohol directly damages the myocardium although abnormalities in cardiac function may only become apparent on exercise. Little is known however about the effect of cirrhosis per se on ventricular function.

We studied 20 patients, 11 with alcoholic cirrhosis and 9 with non-alcoholic cirrhosis. Radioisotope ventriculography was used to assess left ventricular function at rest and in response to exercise using bicycle ergometry.

The increase in cardiac output on exercise was notably impaired (+96% SE ± 9.1) (normal > + 200%) as were the rises in left ventricular ejection fraction (+1.4% S E ± 1.5) (normal > +5%), stroke volume (+25% SE ± 3.5) (normal > +30%) and heart rate (rest 78 bpm SE ± 2.1 to exercise 122 bpm SE ± 4.0) (normal rise to > 150 bpm). End-diastolic volume rose markedly (+23% SE ± 3.7) (normal no change) as did end-systolic volume (+20% SE ± 6.9) (normal fall of 20%). Lactic acid levels rose significantly (0.73 mmol/l SE ± 0.09 to 2.60 mmol/l SE± 0.22). There were no significant differences between alcoholic and non-alcoholic cirrhotics at rest or in response to exercise.

This study clearly demonstrates that left ventricular function is abnormal in cirrhosis regardless of aetiology. Cirrhotic patients have an impaired chronotropic and inotropic response to exercise and use the Frank-Starling mechanism of increased cardiac preload to increase cardiac output. In this way the heart in patients with cirrhosis behaves in a similar manner to the denervated heart. The clinical significance of these findings and their correlates with severity of liver disease requires further investigation.

W104

HEPATOPROTECTIVE EFFECTS OF THE PLANT OSBECKIA OCTANDRA

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For many years an extract of the mature leaves of the plant Osbeckia octandra has been considered by Ayurvedic and other traditional medical practitioners in Sri-Lanka to be beneficial in the treatment of various liver disorders. Previous investigations (Thabrew et al. Planta Med. 53, 239, 1987) demonstrated that O.octandra extract can protect against liver injury induced by carbon tetrachloride (CCl_4). In the present study, the ability of O.octandra leaf extract to protect freshly isolated rat hepatocytes against injury induced by D-galactosamine and tert-butyl hydroperoxide (TBH) was investigated in order to determine whether this plant extract can (a) protect the liver against the effects of hepatotoxins other than CCl_4 and (b) has direct protective effects on hepatocytes. When hepatocytes were incubated with galactosamine or TBH in the presence of the plant extract, a significant dose-dependent protection against hepatocyte injury was observed as compared to control incubations with the hepatotoxin alone with maximum protection at a concentration of the plant extract of 500 μg/ml in the hepatocyte incubation medium. At this concentration the plant extract significantly reduced the inhibition of protein synthesis (as assessed by incorporation of ^{14}C-leucine into protein) in hepatocytes incubated with 10 mM galactosamine for 1h by a mean of 25.62 ± 2.98% and decreased the release of lactic dehydrogenase (LDH) and aspartate aminotransferase (AST) enzyme activities into the medium by 61.56 ± 3.44% and 33.11 + 2.63% respectively. With TBH, the plant extract decreased the toxin induced lipid peroxidation (estimated from malondialdehyde formation) by a mean of 29.90 ± 1.07% together with a 46.92 ± 4.55% and 53.83 ± 6.08% decrease in the release of cellular AST and LDH respectively into the incubation medium. Significant protection was also obtained when the O.octandra extract was added to the incubation medium up to 30 min after pre-exposure of the hepatocytes to either galactosamine or TBH. Further studies are required to purify the active components of the crude extract and also to elucidate the mechanisms through which this plant extract exerts its hepatoprotective effects.

W105

NORADRENALINE RESPONSE TO EXERCISE AND AUTONOMIC DYSFUNCTION IN CIRRHOSIS.

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Stress induced Catecholamine rises are a vital survival response. We studied the effect of exercise and autonomic (ANS) dysfunction on Noradrenaline (NA) responses in cirrhosis. 21 patients (mean age 54; M:F, 14:7; 11 alcoholic, 9 PBC, 1 hepatitis; 9 Childs A, 8 B and 3 C) were exercised on a bicycle ergometer. NA was measured at rest and at peak exercise. ANS function was assessed by standard CVS reflex tests. In normal subjects mean NA level rises from 1.5 nmol/l to 9.5 nmol/l on exercise (633% increase). Our subjects had a mean resting NA of 2.54 nmol/l (SD 1.58) which rose to 4.78 nmol/l (SD 2.21) at peak exercise. Resting NA correlated with Childs Pugh score ($r = 0.40$, $p = 0.01$). There was a difference in percentage change in NA between Childs A - 214% and Childs B and C - 63.3% ($p = 0.05$, CI-1, 303). There were no differences between alcoholics and nonalcoholics. 77% had abnormal CVS reflexes. Each patient was assigned an ANS score which was negatively correlated with resting NA level ($r = -0.463$, $p = < 0.05$), there was a trend to negative correlation between ANS score and peak NA. In conclusion, with increasing severity of cirrhosis resting NA is elevated and the response to exercise is reduced. ANS dysfunction negates this trend to elevated NA levels, suggesting impairment of this survival response in some patients.

T107

HELICOBACTER PYLORI INFECTION DECREASES GASTRIC SOMATOSTATIN mRNA IN DUODENAL ULCER PATIENTS

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Helicobacter pylori (HP) infection increases plasma gastrin but the mechanism responsible for this is not known. We investigated whether this is due to a lack of somatostatin, which is a general inhibitor of gastric function. Somatostatin acts locally, so its release cannot be measured directly. We therefore measured gastric mucosal somatostatin mRNA levels by Northern hybridisation, as an indicator of the rate of synthesis.

Methods: 10 patients with duodenal ulcers were studied before and after eradication of HP. 5 antral biopsies were taken on each occasion, snap frozen at -70°C, homogenised in acid guanidinium isothiocyanate and total RNA extracted with phenol/chloroform. After Northern blotting the RNA was sequentially hybridised with ^{32}P-labelled human cDNA probes for somatostatin, gastrin and 18S rRNA to correct for loading differences. Washing was at high stringency and the results are expressed as specific mRNA/rRNA ratios of arbitrary densitometric units.

Results: After eradication of HP the median somatostatin mRNA level increased from 50 (25-160, range) to 95 (40-180), $P < 0.02$. Gastrin mRNA levels were not significantly changed from 32 (19-217) before to 42 (7-118) after treatment.

Conclusion: HP infection in duodenal ulcer patients is associated with decreased antral somatostatin mRNA. This may explain the abnormalities of gastric physiology seen in these patients.

H pylori pathogenesis and treatment T106–T111

T106

Production of fucosidase and neuraminidase by *Helicobacter pylori* and its possible pathogenic role.

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Helicobacter pylori (HP) in human gastric mucosa is found in close apposition to gastric mucus. The mucus glycoprotein is a potentially rich energy source for the organism. We have investigated *HP* for mucin degrading glycosidases.

HP was isolated from gastric biopsies of patients with *HP* gastritis and cultured, harvested, washed and suspended in normal saline and the cell walls disrupted by ultrasonication. Following centrifugation the supernatant was assayed for enzyme activity using the methylumbelliferone-tagged substrates.

HP did not produce any detectable β-galactosidase, α-N-acetylgalactosaminidase or β-N-acetylglucosaminidase but produces α-fucosidase, neuraminidase (sialidase) and α-glucosidase. The fucosidase and neuraminidase were purified by gel chromatography. They had approximate m.w. of 90 kD and 100 kD respectively. The fucosidase and the neuraminidase had a pH optimum of 7 and 7.5 and a Km of 2.31 and 2.79 mmol/l respectively. The activities of the enzymes were: neuraminidase, 163 μmol/min/mg; fucosidase 4.12 μmol/min/mg; α-glucosidase 67.1μmol/min/mg.

HP appears to be able to partially degrade the mucin glycoconjugates as a potential energy source. Its production of both fucosidase and neuraminidase may well be relevant to its pathogenicity since: (i) neuraminidase (sialidase) production is a feature of pathogenicity in enteric organisms and (ii) loss of fucose in gastric mucus (ie. loss of secretor antigen) is associated with an increased risk for duodenal ulcer disease. (iii) *HP* has a gal-galNAc binding lectin on its cell surface, hence sialidase expression may facilitate *HP* binding to the gastric mucosa.

T108

ERADICATION OF *H.PYLORI* WITH CLARITHROMYCIN & OMEPRAZOLE. M Mendelson, R Greaves, R Logan, B Hegarty, J Baron, J Misiewicz. Parkside Helicobacter Study Group, London.

Failure to eradicate *H.pylori* with triple therapy is associated with metronidazole resistant *H.pylori*. Thus eradication regimes not containing metronidazole are needed. Clarithromycin, a new, better tolerated, acid stable macrolide antibiotic has a similar antimicrobial spectrum to erythromycin (*in vitro* MIC_{90} against *H.pylori* = 0.03 μgml^{-1}). The aim of this study was to determine the eradication rate of clarithromycin 500 mg tds and omeprazole 40 mg mane for 2 weeks.

Patients needing *H.pylori* eradication were studied. Before treatment all patients were endoscoped and *H.pylori* status assessed by antral culture (microaerobic conditions, for up to 10 days), antral and corpus histology (H&E / Gimenez stains), and ^{13}C-urea breath test (^{13}C-UBT, European standard protocol, positive result = excess $\delta^{13}CO_2$ excretion > 5 per mil). Compliance was assessed by returned tablet counts. Clearance (a negative ^{13}C-UBT at the end of treatment) and eradication of *H.pylori* 4 weeks after finishing treatment were assessed by the ^{13}C-UBT.

Twenty-five patients (16 men, median age 46 y) with DU (n=17) or duodenitis/NUD (n=8)) all with a positive ^{13}C-UBT (mean (±sem) excess $\delta^{13}CO_2$ excretion = 26.6 (±4.9) per mil) and either positive antral histology (n=24) or positive antral c[illegible] =19) were studied. Before treatment all isolates of *H.pylori* were sensitive to clarithromycin, but 8 isolates were resistant to metronidazole. In 23/25 (92%) the ^{13}C-UBT was negative immediately after finishing treatment. Four weeks later the ^{13}C-UBT was negative in 20/25 (mean (±sem) excess $\delta^{13}CO_2$ excretion = 1.2 (±0.3) per mil, eradication rate = 80%). *H.pylori* was not eradicated in 5 patients, including 1 patient who experienced severe taste disturbance and was unable to complete the treatment. 6 other patients experienced taste disturbance but this was not sufficient to influence compliance.

These results show that this novel treatment regime is well tolerated and with an eradication rate of 80% may provide an alterantive treatment for metronidazole resistant *H.pylori*.