FIRST LINE TREATMENT WITH OMEPRAZOLE 10MG OM IS A MORE EFFECTIVE STRATEGY THAN GAVISCON® 10ML QID IN THE RELIEF OF DYSPHAGIA SYMPTOMS IN PRIMARY CARE.  

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Six hundred and seventy four dyspeptic patients with heartburn and/or epigastric pain as their predominant symptom and who had no proven abnormality (e.g. proven peptic ulcer) to explain their symptoms were blindly randomised to either omeprazole 10mg om or Gaviscon® 10ml liquid 10ml qid for a parallel group study with assessments after 2 and 4 weeks. The primary efficacy variable, percentage of patients with complete symptom relief, was compared between the two groups. Other efficacy variables included the percentage of patients with subjective symptom control (maximum of 1 day of mild symptoms present), patients’ quality of life (psychological general well-being (PGWB) index and the gastrointestinal subjective rating scale (GSRS)) and patients’ subjective assessment of their treatment. Complete symptom relief and sufficient symptom control (defined as at least 2% relief of symptoms in both treatment periods) was compared between the two groups. Other efficacy variables included the percentage of patients with subjective symptom control (maximum of 1 day of mild symptoms present), patients’ quality of life (psychological general well-being (PGWB) index and the gastrointestinal subjective rating scale (GSRS)) and patients’ subjective assessment of their treatment. Complete symptom relief and sufficient symptom control (defined as at least 2% relief of symptoms in both treatment periods) was compared between the two groups.

Comparison of quality of life scores between treatments significantly favoured the omeprazole group at 2 and 4 weeks for the PGWB (p = 0.0002; p = 0.0009 respectively) and the GSRS (both p < 0.0001). For subjective assessments of treatments, at 2 and 4 weeks, a significantly greater proportion of patients rated omeprazole to be more effective in symptom relief (both p < 0.0001) and more convenient to use (both p < 0.0001) compared to Gaviscon. This study demonstrates that, compared to Gaviscon 10ml qid, omeprazole 10mg om is significantly more effective in the management of dyspepsia symptoms and is the patients’ preferred treatment.

MANIPULATION OF INTESTINAL TRANSIT RATE ALTERS COLONIC LUMINAL PH AND STOOL SHORT CHAIN FATTY ACID CONCENTRATION. SI Lewis and KW Heaton. Department of Medicine, Bristol Royal Infirmary, Bristol BS2 8HW. 

Populations at low risk of colonic cancer consume large amounts of fibre and starch (fermented by bacteria to short chain fatty acids (SCFA)) and pass bulky stools. Travelling the colon SCFA are absorbed and luminal pH increases to neutral. One SCFA, butyrate, is the colon’s main energy source and inhibits malignant transformation in vitro. Low colonic pH should be associated with high levels of butyrate and thus decreased predisposition to cancer. We set out to test two hypotheses: 1. Altering colonic transit rate alters colonic pH. 2. Distal colonic luminal pH is correlated with the SCFA (especially butyrate) content of the stools.

13 healthy volunteers took in turn supplements of wheat bran (mean 28.3g/day), senna laxative and loperamide, each for nine days with a 2 week washout period. Before and in the last 4 days of each intervention period dietary intake, whole gut transit time (WGGT), stool pH, stool SCFA concentrations (by GLC) and intracolonc pH (using a radiotelemetry capsule for continuous monitoring) were assessed.

There was no difference between dietary intakes systematically total fibre, NSP or fat at the start and end of each interventional period. pH measurements were similar in the distal colon and stool. WGGT decreased and stool output increased with wheat bran and senna, vice versa with loperamide. Changes in WGGT were least impressive for wheat bran. Baseline stool SCFA concentration correlated with distal colonic pH (r=0.417, p=0.01) and WGGT (r=-0.623, p<0.001), similar correlations were seen for baseline stool butyrate (distal pH r=0.434, p=0.007 & WGGT r=0.610, p<0.001).

There is a relationship between bowel transit rate (diet being constant) and stool pH, stool SCFA concentration and distal colonic pH. This may explain the associations between colonic cancer and dietary fibre, stool output and stool pH, in that stool pH is a marker for SCFA levels including butyrate.

DIFFERENTIAL FAT METABOLISM IN CACHEXIA OF CHRONIC LIVER DISEASE: AN IN VIVO 13C MRS AND GLC STUDY. EL Thomas, JD Bell, ML Barnard, J Sargentoni, BR Davidson, SD Taylor-Robinson, Gastroenterology and Hepatology MR Unit: Hammersmith Hospital, London W12 0NN and University Department of Surgery, Royal Free Hospital and School of Medicine, London NW3 2QG.

Understanding the metabolic changes controlling weight loss in chronic liver disease may allow rationalisation of dietary regimes which aim to ‘build up’ patients prior to orthotopic liver transplantation (OLT). Carbon-13 magnetic resonance spectroscopy (13C MRS) is a non-invasive method of characterising adipose tissue composition. We examined 22 malnourished patients prior to OLT, using 13C MRS of adipose tissue in vivo. Patients were re-examined 6-8 weeks post OLT. Results were compared to 42 healthy volunteers. Subcutaneous and omental adipose tissue were obtained for comparative GLC analysis from 11 patients at OLT and in 4 volunteers undergoing hernia repair. A non-preferential loss of all major classes of fatty acids were found by 13C MRS prior to OLT. Eight weeks post OLT, subjects showed a considerable increase in body mass with a significant alteration in adipose tissue fatty acid profiles on repeat 13C MRS. (18% increase in saturated fatty acids, p<0.01; 6% decrease in unsaturated fatty acids, p<0.01). This may be secondary to the use of essential polyunsaturated fatty acids for biosynthesis of eicosanoids in the postoperative period.

Conclusion: Application of noninvasive MRS techniques may be of use in the future to design the optimal dietary management of cachexia.
SEROLOGICAL SCREENING FOR COELIAC DISEASE INDICATES THAT LATENCY IS UNCOMMON

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We have previously reported the prevalence of overt enteropathy consistent with coeliac disease to be at least 1:140 for the general adult population following a serological screening programme. The "iceberg" concept has been used to describe the wide spectrum of disease activity, from symptomatic to latent and potential coeliac disease.

AIM: To determine if subjects with normal small intestinal histology and positive serology have morphometric or immunohistochecmic evidence of latent coeliac disease.

METHODS: Subjects with positive serology for coeliac disease detected by an international screening programme (MONICA 1991) were followed up 3 years after initial screening and assessed by jejunal biopsy and repeat serology. Pathological specimens were assessed by routine histological analysis, computer-aided morphology and evaluation of T-cell subsets with CD3 and TCR8 monoclonal antibodies. The following groups were compared: ENT (villous atrophy), POS (persistent serology, normal histology) and NEG (positive at screening, negative at follow-up, normal histology). Twenty-one subjects from the MONICA survey with negative serology and normal histology acted as controls (CON).

RESULTS: Biopsies from sixty-six subjects (32 male, mean age 50.4 yrs) were suitable for evaluation. ENT (n=10) had significantly higher intraepithelial lymphocyte counts per 100 epithelial cells (IEL), y6 T-cell and CD3 T-cells per unit length epithelial (p<0.001) and lower villous height/crypt depth (VH/C) ratio (p<0.001) compared to CON (n=21). POS (n=9) had a non-significant reduction in VH/C ratio (13.3±1.35) and IELs (9.09±9) compared to CON. POS and NEG (n=26) did not differ significantly in the various parameters.

CONCLUSIONS: Subjects with persistently positive serology and normal histology at follow-up had no significant morphometric features of latent coeliac disease.

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N-METHYL L-ARGININE AMELIORATES THE ENTEROCYTE DAMAGE SEEN IN COELIAC SMALL INTESTINAL BIOPSIES CULTURED WITH GLUTEN.

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Aims: We wished to determine whether we could detect increased nitric oxide (NO) production in the supernatant of jejunal biopsies from patients with coeliac disease (CD) following in vitro culture with Frazer's fraction III (FFIII) of gluten and whether a NO inhibitor N-methyl L-arginine (LNMMA) could reduce the FFIII induced enterocyte damage.

Methods: Small intestinal biopsies from 10 patients with treated CD and 6 disease controls (DC) were cultured for 18 hours with medium alone (OCM), ovalbumin (OVALB) (1mg/ml), FFIII (1mg/ml), FFIII+LNMMA (1mg/ml) or LNMMA alone. NO production was determined by measuring nitric (NO2) levels using a colorimetric (Griess) reaction. The enterocyte height (MCEH) was calculated by measuring the height of 30 enterocytes of different villi under x40 magnification using a calibrated eyepiece graticule from cryostat sections of the cultured biopsies.

Results: Median IQ range NO2 levels(umol/l) of tissue and enterocyte height:

- Nitrite
  - OCM: 17.0-54
  - FFIII: 48.1-148
  - FFIII+LNMMA: 0-0
- DC: 0-36
- MCEH
  - OCM: 13.6(12.7-15.3)
  - FFIII: 9.5(9.0-10.2)
  - FFIII+LNMMA: 11.7(11.3-14.4)
- CD: 14.4(13.8-15)

The CD biopsies incubated with FFIII produced significantly greater NO2 compared to OCM (p<0.05) and this could be blocked with LNMMA(p<0.001). A reduction in MCEH was seen in CD biopsies cultured with FFIII(p<0.01) compared to OCM and this was prevented by LNMMA(p<0.01). These results were not seen in disease controls or with the internal controls of OVALB and LNMMA alone.

Conclusion: In CD but not controls we have demonstrated significantly raised levels of NO as indicated by raised NO2 in supernatants from patients with CD when incubated with FFIII and an associated reduction in MCEH. These changes could be blocked with LNMMA, an inhibitor of NO. These findings implicate NO in the pathogenesis of CD.

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MONITORING DIETARY COMPLIANCE IN COELIAC DISEASE USING RED CELL DISTRIBUTION WIDTH

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Alteration in Red Cell Distribution Width (RDW) has been suggested to be useful in diagnosing Coeliac Disease as early nutritional deficiency the RDW changes prior to the development of anaemia or a significant change in the mean corpuscular volume. RDW is an expression of the coefficient of variation of red cell scatter (normal 11.6 - 14.0%), derived from the red cell size histogram produced by modern analysers which is centred around the red cells' mean corpuscular volume (MCV). The RDW value is a measure of the percentage of cells which lie outside a range about the MCV, and quantifies the degree of red cell anisocytosis. Normal values indicate a homogenous population of cells, high values a heterogenous population. Correction of nutritional deficiencies should allow normal red cell maturation and return to a normal red cell population, with a simultaneous reduction in RDW.

We reviewed fifty-one consecutive coeliac patients diagnosed since 1987. 76% of patients had an elevated RDW at presentation of coeliac disease. Mean RDW at presentation was 17.3%, significantly higher than after treatment with gluten-free diet when mean RDW was 13.8% (p<0.001 ). The initial rise in RDW was independent of the cause of nutritional deficiency i.e. iron, B12 or folate deficiency, as was the subsequent fall in RDW (p<0.05 ). Thirty-nine patients had had their endomysial antibody (EMA) measured at the same time as a full blood count, we found that when the EMA was positive, the mean RDW was 16.4%, whereas when negative the mean RDW was significantly different at 13.8% (p<0.001 ).

In summary, red cell distribution width correlates with nutritional deficiency and antibody status in coeliac disease and can be used as a simple means of monitoring dietary compliance.

NOVEL DIFFERENTIALLY-EXPRESSED GENES IN COELIAC DISEASE IDENTIFIED BY DIFFERENTIAL DISPLAY

REVERSE TRANSSCRIPTION PCR

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There are many important questions in the pathogenesis of coeliac disease which remain unanswered including how the mucosal changes are produced and what factors, in addition to HLA susceptibility genes, are required to develop the disease. We have examined mucosal biopsy samples by means of the differential display reverse transcription PCR technique in order to identify previously unrecognised genetic factors. This involves the construction of an mRNA transcription profile which can be compared between coeliac and control populations.

Patients and Methods: Duodenal mucosal biopsies were obtained from 25 control patients (histologically normal) and from 25 patients with coeliac disease with varying degrees of histological abnormality. These were immediately snap frozen in liquid nitrogen and total RNA was extracted. The samples were reverse transcribed using twelve separate anchored oligo-dT oligonucleotide(Oligo dTN23) primers to ensure that each mRNA species was transcribed to cDNA. Each of these products was amplified by PCR using one of 26 arbitrary 10mer primers and one oligo dTN23 primer to ensure that each transcript was amplified for further study. Products were then performed on a 6% polyacrylamide-urea gel and the transcription profiles of controls and coeliac patients compared. Bands which corresponded to differentially expressed transcripts were cut out, reamplified and then sequenced.

Results: Four differentially expressed mRNA species have been identified and sequenced. Of these, one is a 291 base pair mRNA which has at present only been seen to be expressed in coeliac patients and has no significant homology to known genes on searching DNA databases. The other three mRNA species show stronger expression in coeliaics than controls and again show no significant homology to known genes.

Conclusions: The identification of differentially-expressed genes may be important in disease pathogenesis and these genes are now being further characterised by northern blotting and chromosomal localisation.
CFTR gene mutations in chronic pancreatitis.

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The perception of pancreatic damage in cystic fibrosis (CF) as an accelerated form of chronic pancreatitis (Am. J. Path. 1982, 105, 99-121) suggests that aberrant function of the CFTR protein may be involved in the pathogenesis of the acquired disease. Accordingly DNA extracted from bucal washing of 126 consecutive patients with chronic pancreatitis was examined for 22 CFTR mutations that together account for 95% of the mutations in the North West of England.

Eighteen patients, 14% carried a single CFTR mutation compared to the local population carrier rate of 5% (95% CI 8 - 20%; p < 0.0001). The frequency of the AF508 mutation was similar to that observed in the general population. The length of the intron 8 polymerase sequence (577-779) in the exon acceptor site region was also characterised, as the 575 frame is known to reduce levels of functional mRNA and hence the protein. The 575 allele was identified in 23% of patients with a CFTR mutation, and in 5% of those without a mutation (95% CI 3 - 44%; p < 0.01).

Patients with a CFTR mutation were younger than the others at presentation (median 21 vs 34 years; p < 0.05) and among them fewer drank alcohol in excess (p < 0.05) or smoked cigarettes (p < 0.05). Pancreatogram abnormalities, calculi, pancreatic insufficiency and glucose intolerance were equally represented in the two subgroups.

These findings support the hypothesis under test and offer an explanation for the heterosexual trend inferred from the report of a family in which cystic fibrosis and chronic pancreatitis coexisted.

Initial study of surgical intervention in a new model of severe acute pancreatitis.

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No satisfactory model has been described which accurately simulates human acute pancreatitis complicated by pancreatic necrosis. Increasing severity is usually associated with increasing mortality, which prevents observation of late development of local complications. AIM: To characterise the clinical course, complications and effect of surgical intervention in a new model of acute pancreatitis developed in this unit.

Initial studies have demonstrated this to be a reliable model with no mortality resulting in necrosis of the pancreatic tail and transient oedematous pancreatitis in the head. METHOD: Eight juvenile pigs (25kg) were anaesthetised and central venous access was established. The tail of the pancreas was desvascularised until it became ischaemic with tissue oedema readings of the tail half that of the head. The pancreatic duct was then cannulated and injected with a 50:50 mixture of bile and duodenal washings to result in acinar staining. Serial measurements of the following data were made from Day 0 till Day 28: Respiratory Rate (RR), Heart Rate (HR), Temperature, FBC, U&Es, Glucose, Calcium, LFTs, Lactate, Blood Cultures and CRP. At Day 14, a laparotomy was performed for drainage of collections and pancreatic sampling for microbiology and histology. All animals were killed by Day 28 when the pancreas, liver, kidneys & lung were removed for histological examination. RESULTS: All animals developed pancreatitis with peak serum amylase and CRP at 48hrs, and peak WCC at 96hrs. CRP and WCC also peaked 48hrs after laparotomy. Increased RR and HR were observed between day 1 and 5 following the second laparotomy. Pancreatic necrosis was found in all tails (4 infected) with cyst formation in 2 and abscess in 2, requiring drainage. There were no deaths from pancreatitis. CONCLUSIONS: A reproducible large animal model of complicated pancreatitis has been developed which survives for up to one month and allows for repeated blood sampling, physiological measurements and surgery. In its clinical course, biochemical profile, and incidence of complications, it closely simulates human acute necrotising pancreatitis. It is therefore a suitable model for surgical and pharmacological intervention studies.
A COMPARATIVE STUDY OF MINIPROBE INTRADUCT ULTRASOUND AT ERCP, ABDOMINAL US & SPRAIL CT IN THE STAGING OF PANCREATICOBILIARY TUMOURS.


We have previously reported the results of our initial experience in visualizing biliary, ampullary and pancreatic head tumours using intra-duct ultrasonic (IDUS) with high frequency min probes in 44 patients (pts) at the time of ERCP. We now report the results of staging these types of tumours with IDUS, abdominal US and spiral CT scanning.

Patients and methods: From May to November 1995 19 pts (mean age 56 years, range 26-75 yrs) with clinical or biochemical pancreatitis or ampullary tumours were studied. 23 of these pts were investigated with spiral CT (16 min probes, ampulla (n=4) and head of pancreas (n=5)). 2 patients with a history of previous abdominal surgery were not studied. The results were compared with histological results at surgery.

Results: The tumour (mean size 2.7 cm, range 1.2-6) was visualized by IDUS in all 15 pts, but missed by US in 7 and by CT in 2. The tumour stage was upgraded by CT compared with US in 8 pts and by IDUS compared with US & CT in 5 pts. There was no down-grading of the tumour stage by IDUS compared with US & CT. In 4 of 5 pts with pancreatic head cancers it was technically impossible to completely stage lesions eccentric to the bile duct by IDUS. This was due to low penetration (usually 2-2.5 cm) and periductal infiltration, which were seen well with US or CT, but could not be demonstrated. In 4 of 5 pts, who had subsequently had surgical resection, the tumour stage with IDUS was accurately graded (1 cholangiocarcinoma, 3 ampullary neoplasms) and one pancreatic cancer was understaged. With US & CT only 1 cholangiocarcinoma and one ampullary neoplasia were accurately graded and the other 3 tumours underestimated. There were no IDUS or ERCP related complications. Transluminal miniprobe scanning was separately performed in 3 patients to better visualize pancreatic tumours.

Conclusions: Biliary IDUS is better than US & spiral CT at visualizing biliary, ampullary and pancreatic head tumours. Biliary & ampullary tumour staging was underestimated by US & spiral CT compared with IDUS, which also correlated more accurately with the histological findings after resection. With the limited range of current miniprobe, IDUS of the biliary tree appears to be inappropriate for staging of pancreatic head tumours although further developments may improve this.

SYMPTOMS OF GALLSTONE DISEASE: FIVE YEARS AFTER LITHOTRIPSY OR CHOLECYSTECTOMY.

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A trial in which the treatment of 163 patients with gallstones was randomised to either lithotripsy or cholecystectomy was reported in 1992. When symptoms and general health were assessed 1 year after treatment the unexpected findings were that both groups of patients had significant health gains, and that no difference in postoperative survival was observed between patients who had been treated by lithotripsy or those who had undergone surgery.

Patients were therefore randomised in three groups: a) lithotripsy alone, b) cholecystectomy, c) lithotripsy with subsequent cholecystectomy.

Health status assessed by the Nottingham Health Profile (NHP) was similar at baseline and at 1 and 5 years in patients treated by cholecystectomy or by lithotripsy alone. However, the subgroup of patients who were randomised to lithotripsy but subsequently had cholecystectomy had higher NHP scores, indicating more severe symptoms, before treatment than those from either of the other groups (PAIN a) 14.3, b) 23.5 ) 33.1, ENERGY a) 27.7, b) 28.4, c) 43.1).

These higher scores persisted at 1 and 5 years after treatment, despite the intervening cholecystectomy.

Pain was also measured by Visual Analogue Symptom scale (VAS). It was less severe, shown by a lower mean score, 5 years after treatment in both lithotripsy (69.5-56.5), and cholecystectomy groups (65.5-56.1), but patients who had both treatment had a higher score at 5 years than before treatment (57.7-67.8). The VAS score for vomiting was also greater at 5 years in this group [a) 43-39.5, b) 46.8-30, c) 52.7-63.2].

These results show that the health gain seen 1 year after lithotripsy or cholecystectomy persisted for 5 years. Some patients will have a good symptomatic response, whichever treatment is used. However, there is a second group of patients who will continue to have abdominal symptoms in spite of treatment. Further studies are being carried out to characterise patients in the second group, as their symptoms might worsen after treatment.