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WHEN IS A RECTOCELE SIGNIFICANT?

Kumar D, Benson M*, Grant E, Britton A#, Gains G#, Jazrawi R*, Joseph A#. Departments of Colorectal Surgery, Gastroenterology* and Radiology#, St George's Hospital, Tooting, London, UK.

Rectoceles are commonly investigated by barium proctography This is a qualitative investigation and does not provide data on rectocele emptying. We have used a quantitative method [isotope defaecography (ID)] with the aim of differentiating between significant (SR) and non-significant rectoceles (NSR).

We studied 95 patients with a clinical diagnosis of rectocele. ID was performed using 100 Mbq of ^{99m}Tc mixed with 100 mls of oat porridge. 71 of the 95 patients were found to have a rectocele. The percentage and rate of evacuation (%/sec) and also the percentage of isotope retained in the rectocele were calculated. Patients with 15% or more retention in the rectocele were defined as having a significant rectocele.

Results: 34 of 71 had a significant rectocele. The SR group had a significantly higher retention of the isotope than NSR [22.3 (1.4) vs 9.6 (0.4), $p<0.0005$). Similarly the retention of the isotope as percentage of final rectal content was significantly higher in the SR than NSR group [52.6 (2.4) vs 33.1 (1.8)], $p<0.0001$]. The rate of evacuation in the two groups was similar [0.97 (0.1) vs 1.3 (0.1), $p>0.05$]. There was no significant difference in the total percent evacuation between the no rectocele and NSR groups. There was a significant correlation between the presence of a significant rectocele and total percentage evacuation ($r=0.61$, $p<0.0001$). There was no significant correlation between the presence of a SR or NSR and the rate of evacuation.

These data suggest that retention of 15% or more of the rectal contents in the rectocele influences the total percent evacuation resulting in impaired defaecation. This may be a useful way of differentiating between significant and non-significant rectoceles and selecting patients for surgical therapy.

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DETECTION OF FAECAL INCONTINENT EPISODES USING A NEW AMBULATORY WETNESS DETECTOR

J. Gunn, R. Farouk, J.R.T. Monson, G.S. Duthie ; University of Hull, Academic Surgical Unit, Castle Hill Hospital, Cottingham, North Humberside.

Internal anal sphincter ambulatory assessment has suggested the anorectal pressure gradient may be reversed during faecal soiling. However patients are commonly unable to perceive these events. The aim of this study was to develop a wetness detector that would allow us to identify objectively episodes of faecal incontinence.

The wetness detector was constructed from a 5mm catheter with two copper electrodes set 3cm apart. A low voltage AC current was passed down the catheter and when the moisture levels increased, then electrical resistance between the two electrodes would reduce allowing an increase in conductivity indicating faecal incontinence. Simultaneous anorectal manometry was performed to correlate these events with changes in the anorectal pressure gradient.

10 patients (median age 58, range 44-76) with faecal incontinence were assessed for a median of 8 (4-18) hours. Episodes of faecal leakage were detected in all patients characterised by a rise in conductivity. A positive recto-anal pressure gradient was recorded for all of these events.

In conclusion, a sensor has been developed which can accurately and objectively detect episodes of faecal incontinence. The ability to detect occult episodes of faecal leakage has clear implications for the assessment of patients complaining of faecal incontinence.

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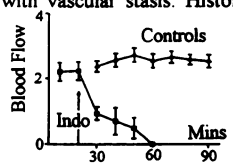
EARLY INDOMETHACIN LESIONS IN RAT JEJUNUM: REDUCED FOCAL BLOOD FLOW AND SHORTENING OF VILLI PRECEDE ULCERATION.

D. Kelly, C. Piasecki, A. Anthony, RE Pounder, AJ Wakefield. Royal Free Hospital and Medical School, London. UK.

Background. Histologically, administration of indomethacin (indo) causes villus shortening, eosinophil infiltration and microvascular distortion, prior to ulceration. These changes may compromise blood flow and lead to mucosal necrosis.
Aim. This hypothesis was tested by correlating histological changes with changes in villus blood flow, measured in-vivo using ulcerogenic doses of indo.
Methods. In two groups of rats (n=5per group), oral indo (15mg/Kg) was given at 4 or 6 h preoperatively. Luminal and plasma levels were measured in order to determine the optimum dosing for subsequent experiments. After anaesthesia, exteriorised villi enclosed in a chamber, were observed by fluorescent microscopy using iv FITC dextran and labelled red cells. Blood flow in surface arcade vessels was calculated from measurements of velocties and diameters ($bf=\pi/4.v.d^2$). In other groups indo was applied by simultaneous topical (100μg/ml) and iv administration (producing a peak plasma level of 100μg/ml) (n=5). Controls consisted of vehicle alone (n=5). Animals were sacrificed, perfusion fixed with 5% formol saline and processed for histology.
Results. Oral indo resulted in peak luminal and plasma indo concentrations of 100μg/ml. In-vivo observation revealed groups of villi with vascular stasis. Histologically the villi were shortened, and had distorted epithelium and vessels. Combined topical and iv indo, given per-operatively, induced immediate progressive slowing of blood flow in individual villi, and complete stasis within 15- 45 mins in individual villi in all animals (Fig). Blood flow in adjacent villi was normal. At this time point, histology showed groups of shortened villi with distortion (but no loss) of surface epithelium overlying foci of vascular stasis, and normal surrounding villi. In both regimens lesions occurred only on the mesenteric border between vasa-recta. All control animals had normal blood flow (2.6 ± 0.1 nl/min) for 1.5hrs.



Conclusions. Oral dosing with indo, or combined topical and iv dosing at an ulcerogenic level, produces pre-ulcerative villus shortening, associated with severe focal interference of capillary blood flow. Thus focal ischaemic changes are likely to be involved in induction of lesions

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SERUM SUCROSE. A NEW SCREENING TEST FOR COELIAC DISEASE.

M A Cox, T H Iqbal, K O Lewis, B T Cooper.
Gastroenterology Unit, City Hospital, Dudley Road, Birmingham. B18 7QH.

An accurate non invasive test to screen for coeliac disease (CD) would be popular with patients and reduce the need for small bowel biopsy. Until recently such tests were inaccurate. IgA endomysial antibodies have been found to have a high sensitivity and specificity for CD. Small intestinal permeability tests involving urinary recovery of ingested markers are highly sensitive but not specific for CD.During the development of techniques to measure permeability in serum, an unidentified peak was found in the serum from untreated CD patients but not in other sera. This peak was later found to be sucrose. The aims of this pilot study were to determine if serum sucrose is a marker for untreated CD and to compare the results with endomysial antibody titres. 20 consecutive newly diagnosed coeliacs, 15 celiacs on a strict gluten free diet for more than 12 months and 15 healthy normal controls were studied. All were given a drink containing approximately 8g of sucrose and had blood taken 30-45 minutes later: serum was deproteinised using the method of Somogyi and analysed using HPLC and pulsed amperometric detection for the presence or absence of sucrose (Proc Ass Clin Biochem 1995 A82:89-90). Sucrose was present in all 20 untreated coeliacs but in none of the treated coeliacs or normal controls. 17 untreated coeliacs were endomysial antibody positive; all the treated coeliacs and normal controls were negative. Serum sucrose separated untreated coeliacs from treated coeliacs and normal controls more accurately than endomysial antibodies. Serum sucrose shows promise as an indirect marker of villous atrophy and coeliac disease.

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MICROALBUMINURIA IN TREATED ADULT COELIAC DISEASE.

XA McFarlane[1], F Havard[2], DAF Robertson[1], P O'Hare[2]. Departments of Gastroenterology[1] and Diabetes[2], Royal United Hospital, Combe Park, Bath. BA1 3NG.

Background. We have observed that of 19 adults (13 males) with microalbuminuria (urine albumin excretion 20 to 200 µg/minute) associated with insulin dependent diabetes mellitus (IDDM), 3 (16%) male patients had coeliac disease (2 newly diagnosed patients, each investigated because of unexplained anaemia, and 1 patient with coeliac disease diagnosed and treated with gluten free diet since age 5 years). We have therefore investigated the level of urinary albumin excretion in patients with treated coeliac disease compared with healthy adults.

Methods. 36 patients with treated coeliac disease (average age 48.3 years average duration of gluten free diet [GFD] years) and 30 healthy volunteers (average age 40.2 years) were recruited. None of the patients or volunteers had diabetes mellitus. A 2 hour morning urine collection was obtained from patients and volunteers, and urine albumin (mg/l) and creatinine (mmol/l) concentrations measured using standard laboratory techniques. Results were expressed as albumin creatinine ratio (A/C ratio: mg/mmol).

Results. A/C ratio was significantly higher in patients than controls (0.99 c.f. 0.65 mg/mmol. $p<0.02$, unpaired t test). There was no correlation between A/C ratio and duration of GFD ($r=0.14$, Spearman's rank correlation). There was no difference in A/C ratio (0.89 cf 1.03 mg/mmol) in patients who had strict GFD ($n=27$) compared with those with occasional intake of gluten.

Comments. 1) Patients with treated coeliac disease have significantly increased urine albumin excretion. The clinical and prognostic significance of this remains to be determined. 2) The incidence of coeliac disease is known to be increased in IDDM, but perhaps those IDDM patients with microalbuminuria are particularly likely to have hitherto undiagnosed coeliac disease.

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BILE ACID MALABSORPTION IN PERSISTENT DIARRHOEA: THE DISTRICT GENERAL HOSPITAL PERSPECTIVE

M Smith, P Cherian, GS Raju, B Dawson, S Mahon, KLE Dear, KD Bardhan. Rotherham General Hospitals NHS Trust, Moorgate Road, Rotherham, UK S60 2UD

INTRODUCTION Bile acid malabsorption is now known to cause chronic diarrhoea but is widely perceived to be rare, requires complex assays of faecal bile acid excretion for its diagnosis and so is recognised mainly in specialist centres. The SeHCAT retention test, however, now allows for the easy quantification of bile acid absorption and can be done in most district hospitals.

PRINCIPLE & METHOD OF SeHCAT TEST ^{75}SeHCAT is homotaurocholic acid labelled with the gamma emitter ^{75}selenium. This synthetic bile acid accurately tracks the path of natural bile acids through the enterohepatic circulation. A 37KBq dose is given, baseline counts over the body recorded (with a gamma camera) and then re-recorded 7 days later. Retention <10% indicates bile acid malabsorption, and relief of diarrhoea by bile acid sequestrants, cholestyramine or colestipol, confirms the diagnosis.

PATIENTS n=126 with chronic diarrhoea. Positive controls: Crohn's disease with ileal resection & in clinical remission (CONT) n=18; Crohn's disease in clinical remission (CD-R) n=18; ulcerative colitis (UC) in remission n=4; gastric surgery ± cholecystectomy (GAS SURG) n=18; diarrhoea predominant irritable bowel syndrome (IBS) n=68.

RESULTS *Incidence of malabsorption* CONT 18/18; CD-R 13/18 (72%); UC 1/4; GAS SURG 12/18(67%); IBS 22/68(32%). ***Bile acid malabsorption: control of diarrhoea with conventional treatment*** (prednisolone ± ASA drugs; anti-diarrhoeals): CONT 8/18; CD-R 10/13; UC 1/1; IBS 3/18. ***Outcome of treatment with bile acid sequestrants*** Those failing on anti-diarrhoeal and anti-inflammatory drugs were treated with cholestyramine or colestipol. Diarrhoea was controlled in: CONT 8/10, CD-R 3/3; GAS SURG 3/6; IBS 14/15

CONCLUSIONS Bile acid malabsorption is common in patients with chronic diarrhoea, including IBS, and is easily detectable by SeHCAT retention. Treatment with bile acid sequestrants is effective and particularly useful when conventional anti-inflammatory drugs and antidiarrhoeals fail.

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REVERSAL OF SECRETION IN HUMAN CHOLERA MODEL BY 5-HT$_3$ ANTAGONIST, GRANISETRON.

JL Turvill, FH Mourad, MJG Farthing. Digestive Disease Research Centre, St Bartholomew's & The Royal London School of Medicine & Dentistry, London UK.

Introduction. To date most treatments for acute diarrhoea have been aimed at replacing fluid and electrolyte losses, slowing intestinal transit or treating the infection with antibiotics. In animal experiments 5-hydroxytryptamine (5-HT) has been implicated in cholera toxin (CT)-induced secretion and the 5-HT$_3$ receptor antagonist, granisetron, has been shown to reverse 60-70% of intestinal secretion. If this finding were confirmed in humans then 5-HT$_3$ antagonists would emerge as a class of anti-secretory drugs, invaluable in mitigating the severity of diarrhoea.

Aim. This is a placebo-controlled, cross-over study to investigate the effect of granisetron on CT-induced jejunal water and electrolyte transport in male subjects using an established model of human cholera.

Methods. Fasted subjects randomly received 3mg intravenous granisetron during one treatment period and placebo during a separate treatment period. Accurate placement of a triple-lumen perfusion tube in the proximal small intestine was confirmed by fluoroscopy. Two inflatable balloons on the perfusion tube isolated a 30cm closed segment of jejunum into which 20µg CT (Swiss Serum and Vaccine Institute, Berne) was introduced. After 3 hours incubation, perfusion with a plasma electrolyte solution (Na 140, K 4, Cl 104, HCO_3 40mmol/L) containing a non-absorbable marker, [^{14}C]-PEG,was carried out to assess net water and electrolyte movement. 3x10min collections were taken.

Results. CT-induced secretion (median -6.19ml/cm/h [interquartile range -5.28 to -7.01], n=6 was reversed to net absorption by 3mg granisetron (1.31 [2.97 to -1.21], n=8; $p<0.013$). Net chloride secretion (-905.4µmol/cm/h [-818.1 to -987.1]) was reversed to absorption (13.6 [77.4 to -357.1]; $p<0.005$).

Conclusion. This study confirms our previous findings in rat small intestine that 5-HT$_3$ antagonism reverses CT-induced secretion and suggests that granisetron is an effective anti-secretory agent in humans.

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RANDOMISED DOUBLE BLIND PLACEBO CONTROLLED STUDY OF THE ABILITY OF *SACCHAROMYCES BOULARDII* TO PREVENT ANTIBIOTIC RELATED DIARRHOEA

L Potts, SJ Lewis, R Barry; Department of Medicine, Bristol Royal Infirmary, Bristol, BS2 8HW England.

INTRODUCTION Diarrhoea is a common side effect of antibiotic therapy, especially in the elderly. As well as the significant morbidity and mortality associated with diarrhoea in this age group there is an increased work load put upon the staff attending to such patients. *Saccharomyces boulardii* is a non pathogenic yeast. Several studies have demonstrated its ability to reduce the frequency of diarrhoea in patients with pseudomembranous colitis, AIDS, and children with diarrhoea or on enteral feeding. We set out to asses its role in preventing antibiotic related diarrhoea.

METHODS Consecutive patients admitted to medical wards over the age of 65 who were prescribed antibiotics, were randomised to receive either *S boulardii* 113g bd or placebo for as long as they received antibiotics. Bowel habit was monitored using a record of interdefecatory intervals (IDI) and stool form graded 1 to 4 (hard to liquid). Stool samples were analysed every fourth day for *Clostridium difficile* toxin. The data was analysed using Student t tests.

RESULTS Of the 64 patients randomised to *S boulardii* or placebo there was no difference in sex, age, duration of antibiotic use, length of hospital stay, IDI, stool form, presence of *C difficile* toxin, the amount of patients receiving laxatives or the amount of patients experiencing watery stools. No side effects were attributable to *S boulardii*.

Mean (sd) values for patients receiving *S boulardii* or placebo

Mean values	Active group n=32		Placebo group n=30	
Age	77.4	9.3	75.6	6.6
Length of treatment (days)	8.4	4.2	8.5	6.7
Length of hospital stay (days)	10.9	6.1	11.7	7.8
IDI (h)	29.4	18.1	25.9	12.4
Stool form	2.08	0.6	2.24	0.7
Presence of *C difficile* toxin	5		3	
no of patients who used laxatives	7		5	
no of patients with diarrhoea	6		5	

CONCLUSION There was no evidence that the concomitant use of *S boulardii* with antibiotics alters patients bowel habits or the presence of *C difficile* toxin in the stool. Thus further evaluation of *S boulardii* is needed before it can be recommended as a 'natural cure' for the prevention of antibiotic related diarrhoea

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BASAL GASTRIC pH AND DUODENAL BACTERIAL COLONISATION IN HUMAN IMMUNODEFICIENCY VIRUS POSITIVE (HIV+) PATIENTS WITH AND WITHOUT DIARRHOEA.

P.J.Neild, M.Hannan, D.Sharpstone, B.Azadian, B.G.Gazzard. Chelsea and Westminster Hospital, London, U.K.

Hypochlorhydria and depressed mucosal immune function may predispose HIV+ people to bacterial colonisation of the small bowel. We tested the hypothesis that such overgrowth is present, and commoner in those with diarrhoea and/or weight loss. **Methods:** 43 fasted HIV+ subjects,29 of whom had chronic diarrhoea, and 8 HIV- controls underwent oesophagogastroduodenoscopy (OGD). Biopsies were examined for opportunistic enteric infections, and gastric aspirate analysed for basal gastric pH. Duodenal aspirates, taken under sterile conditions, were processed, using a semiquantitative technique, on standard aerobic and anaerobic laboratory media. **Results:** 15 (34.8%) of HIV+ subjects had bacterial overgrowth ($>1x10^5$ CFU/ml), 10 (34.5%) with diarrhoea (D) and 5 (35.7%) without diarrhoea. (ND). The commonest organisms were those of oral flora, Pseudomonas sp. and E coli. No anaerobes were identified. No controls had bacterial overgrowth. Absolute bacterial count was increased in HIV+ subjects compared with controls and significantly so in those with diarrhoea.. There was no relationship between bacterial overgrowth and antibiotic use. There was no significant correlation between bacterial count and either gastric pH (r=-0.05), which was similar in all groups, or % weight loss (r=0.07); or between CD4 and either bacterial count (r=0.07) or gastric pH (r=-0.26). However, all subjects with pH>4 (23.3%) had CD4<50.Values expressed as median (range).*p<0.05 HIV+ vs controls

	Controls	HIV+/D	HIV+/ND
basal gastric pH	3(1.3-3.6)	2.5(0.5-7.4)	1.75(1.1-5)
bacterial count	0(0-720)	$1x10^4$($0-2x10^7$)*	$4.7x10^3$($0-1x10^7$)
no. on antibiotics	0	18(62%)	8(57%)

Conclusions: bacterial colonisation occurs in HIV+ individuals and appears unrelated to either gastric pH, weight loss, or stage of disease. It is unlikely that small bowel bacterial overgrowth is a cause of 'pathogen negative' diarrhoea in HIV infection.

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ENTEROCOCCUS FAECIUM STRAIN PR88 - AN EFFECTIVE PROBIOTIC.

Hunter J.O., Lee A.J., King T.S., Barratt M.E.J., Linggood, M.A., Blades J.A. Department of Gastroenterology, Addenbrooke's Hospital, Cambridge and Unilever Research Laboratory, Sharnbrook, Beds.

The concept of administration of non-pathogenic bacteria (probiotics) to improve colonic fermentation has a long history but little scientific credibility. Enterococcus faecium may be a commensal in the healthy human gut and PR88 is a distinct strain which does not possess markers of pathogenicity including haemolysin, hyalouronidase or thermonuclease. Early weaning of piglets lead to transient partial villous atrophy, malabsorption and weight loss. Administration of PR88 10^7 - 10^9 organisms daily from 1 week of age had a dose-related effect in preventing these changes. As secretory diarrhoea is associated with increased cyclic-AMP production, this was examined in K-1 cells from the Chinese hamster ovary. Pre-treatment with PR88 prevented elevation of cyclic AMP after administration of isoproterenol, forskolin and E coli heat labile enterotoxin. A 90 day feeding trial of 10^{11} organisms per day in rats revealed no harmful effects. To assess the viability of PR88 in the human gut 10^{10} organisms per day were administered for 12 weeks to 28 patients with high volume diarrhoea caused by food intolerance. PR88 was identified in the stools of all subjects at counts of 10^8 per gram. As PR88 counts rose, there was a corresponding drop in Strep faecalis excretion which reversed when PR88 feeding stopped, PR88 being lost from the stools of virtually all subjects within 2 weeks. No effect on enterobacteria or total anaerobes were detected and haematological and biochemical screening remained normal. There was no serum antibody response to PR88. Symptoms improved in 19 subjects and faecal weights fell from 912 ± 679g to 610 ± 400g (p = 0.0005). Further clinical studies of PR88 are indicated.

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EFFECT OF SEX, ORGANISM, AND DURATION OF ILLNESS ON THE DEVELOPMENT OF POST DYSENTERIC IRRITABLE BOWEL SYNDROME (IBS).

J.M. Hebden[1], R.C. Spiller[1], K.R. Neal[2]. Depts. of Gastroenterology[1] and Epidemiology[2], University of Nottingham Medical School, UK.

Although postdysenteric irritable bowel syndrome (IBS) is well recognised the risk following bacterial gastroenteritis has not been quantified. The statutory notifications system was used to identify 665 people with gastroenteritis. A questionnaire covering medical history, the episode of gastroenteritis, bowel habit now and 12 months ago was mailed 6 months after the notification date. IBS was defined using the Rome criteria. Paired t-tests were used for analysis of symptoms before and after gastroenteritis and logistic regression to estimate relative risk (RR) and 95% confidence limits (CL). 436 questionnaires (66%) were returned.

Using the strict Rome criteria 28 people (7%) had developed IBS for which the risk factors were female sex RR= 2.9 (95% CL= 1.2-6.9) and duration of gastroenteritis RR= 2.1 (95% CL= 1.3-3.4) for each week of symptoms. The number of cases of new IBS by infecting organism were campylobacter 17/228, salmonella 3/104, shigella 3/15*, giardia 1/10 and cryptosporidium 3/10*; * p < 0.05 vs. salmonella.

Lesser changes in bowel habit were surprisingly common being reported in 107 patients. The mean±sem of the number of days per week on which symptoms were experienced are shown below. Table.

symptom	loose stools	bloating	slime	hard stools	urgency
before	0.9±0.2	1.3±0.2	0.3±0.1	1.5±0.2	0.7±0.2
after	2.4 ±0.2	2.5±0.3	1.0±0.2	1.4±0.2	1.7±0.2
p value	<0.001	<0.001	<0.001	n.s.	<0.001

In conclusion, 25% reported altered bowel habit largely characterised by increased frequency of loose stools. IBS developed in 7% of patients. Infection with shigella and cryptosporidium were more likely to result in IBS than salmonella. Female sex and increasing duration of illness significantly increased the risk of developing IBS.

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INHIBITION OF ACID SECRETION BY INTERLEUKIN-1β AND TUMOR NECROSIS FACTOR-α IN CULTURED RABBIT PARIETAL CELLS INVOLVES MULTIPLE PATHWAYS

Ian L. P. Beales and John Calam
Gastroenterology Unit, Royal Postgraduate Medical School, London, UK

The pro-inflammatory cytokines interleukin-1β (IL 1β) and tumor necrosis factor α (TNFα) are potent inhibitors of gastric acid secretion when administered *in vivo*. The site and mechanism of action is not yet understood. Therefore we have studied the effect of these two cytokines on the acid secretory capacity of parietal cells.

Methods: Rabbit parietal cells were isolated by collagenase-EDTA digestion, enriched by centrifugal elutriation and cultured for 40 hours. Intracellular accumulation of ^{14}C aminopyrine (AP) over 30 mins was used to assess acid secretion in response to receptor dependent or independent stimuli.

Results: Both IL 1β and TNFα (0.1-100ng/ml) dose dependently inhibited AP uptake stimulated by 0.1 mM histamine (maximal inhibition IL 1β 23±5.1% p<0.01,TNFα 21±5.6% p<0.05), 0.1 mM carbachol (IL 1β 47±4.4%, TNFα 57±9.2% both p<0.001) and 0.1 μM gastrin (IL 1β 66±14%,TNFα 57±8% both p<0.01). Near maximal inhibition occurred with 10 ng/ml of cytokine. Inhibition was maximal with 15 mins preincubation but was seen at all time points up to 18 hours. There was no alteration in binding of ^{125}I-gastrin or ^3H-histamine. Both cytokines at 10 ng/ml also inhibited AP uptake stimulated by 10μM forskolin (IL 1β 14±2%,TNFα 16±4.5%: both p<0.05) and the calcium ionophore A23187 (1μM) (IL 1β 47±5%,TNFα 65±16 % p<0.001). but had no effect on stimulation by dibutyryl-cAMP. The inhibition of histamine and forskolin action by both cytokines was completely blocked by pretreatment with pertussis toxin (200ng/ml) but this had no effect on inhibition of carbachol or A23187 stimulation. Pretreatment with the tyrosine kinase inhibitor herbimycin A (1μM) also abolished the inhibition of histamine and forskolin stimulation and significantly reduced the inhibition due to TNFα with carbachol and A23187 but had no effect on IL 1β inhibition of these stimulants.

Conclusions: IL 1β and TNFα directly inhibit parietal cell function by multiple pathways, including inhibition of adenylate cyclase and also further steps downstream of the Ca^{++} signalling pathway. Inhibition involves tyrosine kinase dependent and independent pathways.