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A PROSPECTIVE RANDOMISED CONTROLLED CLINICAL TRIAL COMPARING SANDOSTATIN (SMS) AND INJECTION SCLEROTHERAPY IN THE CONTROL OF ACUTE VARICEAL HAEMORRHAGE: AN INTERIM REPORT.

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Recent studies have indicated that somatostatin is a safe effective treatment for the control of acute variceal haemorrhage (AVH). Since SMS a synthetic analogue of somatostatin is relatively inexpensive compared to the naturally occuring hormone, the aim of this study was to compare the efficacy of SMS with injection sclerotherapy (IS) in the control of AVH. Forty consecutive patients admitted with endoscopically proven severe AVH were randomised to either IS or a continuous infusion of SMS (50ug/h) for 48 hours. The aetiology of the portal hypertension was similar in the two groups as was the distribution of the patients among the categories of the Child's classification. Twenty patients received SMS and twenty IS. Overall control of bleeding was achieved in 18/20 patients receiving SMS and 18/20 patients randomised to IS (p = 0.70 Fischer's Exact Test). SMS was equally effective as IS in controlling AVH in patients with mild, moderate and severe disease and those actively bleeding at the time of their diagnostic endoscopy. Mortality was not significantly different between the two groups of patients. The results of this trial suggest that SMS is: 1) a safe and effective stop-gap treatment for the control of AVH and 2) may be as efficacious as IS although at this stage a type 2 error cannot be excluded.

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SEROTONIN-INDUCED INTESTINAL ELECTROLYTE TRANSPORT: EVIDENCE FOR A CYCLOOXYGENASE-INDEPENDENT PATHWAY IN RAT DISTAL COLON.

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Prostaglandin E_2 (PGE_2) has been implicated as the mediator of serotonin (5-HT) induced intestinal secretion. In contrast, other studies have suggested that the action of 5-HT is independent of PGE_2. Our hypothesis is that 5-HT-induced electrolyte transport is mediated by a direct action of 5-HT at a mucosal receptor and is therefore independent of PGE_2. To test this, rat distal colon (n = 7, consecutive series) was excised and mounted in Ussing flux chambers under short-circuit conditions. Four chambers were run in parallel and after equilibration, the following were added to separate chambers: Indomethacin (IND) 10 nM, 1 μM, 100 μM and no additions (control chamber) and change in short-circuit current (ΔI_{sc} in $\mu A/cm^2$) recorded as an indicator of electrogenic chloride secretion. 100 μM 5-HT was then added and 5-HT-stimulated ΔI_{sc} examined in the presence of IND (a 5-HT only chamber was used as a "positive control").

	ΔI_{sc} in $\mu A/cm^2$ (means ±SEM)		
	5 min	10 min	20min
Control	0.3±1.2	-0.9±1.4	-2.1±1.5
5-HT	24.6±7.1	38.7±5.9	34.3±5.1
IND 10 nM	3.5±4.8	3.6±4.2	1.4±1.6
IND 1 μM	-3.8±1.1	-20.7±6.5	-31.8±6.9
IND 100 μM	-13.4±3.9*	-39.1±10.6*	-51.3±9.8*
5-HT+IND 10nM	29.3±10.5	35.9±6.4	25.9±3.5
5-HT+IND 1 μM	39.3±18.2	48.1±6.4	39.8±9.3
5-HT+IND 100 μM	31.0±4.4	47.0±6.7	42.8±7.4

(*p<0.001 vs control, ANOVA; & p= NS 5-HT vs 5-HT+IND,ANOVA).

The results demonstrate that IND inhibits basal transport in a concentration-dependent manner, suggesting that endogenous eicosanoid activity contributes to transport. 5-HT-induced change in I_{sc} is NOT inhibited by pre-incubation with IND, demonstrating that generation of PGE_2 is not the mechanism by which 5-HT stimulates transport. We conclude that both 5-HT and endogenous eicosanoids stimulate intestinal electrolyte transport but by different pathways and that there is a cyclooxygenase-independent pathway of 5-HT-induced electrolyte transport in this preparation.

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INTERLEUKIN 1 STIMULATES ANION SECRETION IN MAMMALIAN COLON

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Interleukin 1 may have an important role in the pathophysiology of diarrhoeal diseases, however, the precise effect of this cytokine on intestinal secretion has not been established. We therefore investigated the secretory effect and mechanism of action of interleukin 1 in mammalian colon. Stripped rat distal colon was mounted as sheets in modified flux chambers, both surfaces were bathed in Ringers small bowel buffer. Changes in transmucosal short circuit current (Isc), potential difference (pd) and conductance were measured following the basolateral addition of interleukin 1 (10^{-15} - 10^{-5}M), in either chloride free or chloride containing buffer, in the presence of one of the following: (a) no additives, (b) indomethacin 10^{-5}M (cyclooxygenase inhibitor), (c) ICI 207968 10^{-5}M (a lipoxygenase inhibitor), (d) combined (b) and (c), and (e) mepacrine 10^{-5}M (a phospholipase A_2 inhibitor).

Interleukin 1 produced a dose dependent increase in Isc (EC50 = 2 x 10^{-11}M: peak = 47.1 ± 4 $\mu A.cm^{-2}$) and a modest rise in pd and conductance when added to the basolateral, but not the apical half chamber. The change in Isc was attenuated in the absence of chloride (47.1 ± 4 v 9.4 ± 1.1 $\mu A.cm^{-2}$ p<0.001). The Isc was reduced by pretreatment with either indomethacin (cyclooxygenase inhibition) or ICI 207968 (lipoxygenase inhibition) (47.1 ± 4 v 23.8 ± 3.4 : 37.1 ± 4.4 $\mu A.cm^{-2}$ respectively, p<0.01). Moreover, combined pretreatment produced a greater fall in Isc (47.1 ± 4 v 15.3 ± 2.9 $\mu A.cm^{-2}$, p<0.001), but this was further reduced by mepacrine inhibition of phospholipase A_2 (47.1 v 8.3 ± 0.8 $\mu A.cm^{-2}$, p<0.001).

In conclusion interleukin 1 stimulates chloride secretion in mammalian colon. This effect is predominantly mediated by arachidonic acid metabolites, however other phospholipase A_2 derivatives, in particular platelet activating factor, may also be implicated.

F224

WATER SECRETION DURING GUT ANAPHYLAXIS IS REVERSED BY 5-HYDROXYTRYPTAMINE (5-HT) TYPE 2 AND 3 RECEPTOR ANTAGONISTS.

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Exposure of sensitized intestine to specific allergen leads to marked reduction in water and electrolyte absorption. Previously we have demonstrated that 5-HT_3 blockade can partially inhibit these changes. In order to determine whether 5-HT_2 receptors also play a role in this process we studied the effects of 5-HT_2 as well as 5-HT_3 blockade using ketanserin (KET) and granisetron (GRA), singly or in combination, on water flux during gut anaphylaxis.

Hooded Lister rats were inoculated ip with 10μg ovalbumin (OVA) with alum adjuvant; sensitization was confirmed by specific serum IgE titres of >1:8. Intestinal water and electrolyte movement was assessed at 10 min intervals by *in situ* jejunal perfusion, 12 days after sensitization, either with plasma electrolyte solution (PES = Na 140, K 4, Cl 104, HCO_3 40mmol/l) or PES+OVA 20mg/l.

Twenty min after exposure to PES + OVA, net water secretion was observed, compared to absorption with PES alone (median -20μl/min/g [interquartile range -43 to -5], n=11 vs 107 [86 to 113], n=10; p<0.01). Pre-treatment with KET 200μg/kg sc (n=7) or GRA 300μg/kg sc (n=8) partially inhibited the secretory response to PES + OVA (18 [11 to 48] and 13 [6 to 32] respectively; both p<0.01 compared to PES + OVA control); simultaneous administration of KET and GRA had no additive effect (25 [13-44], n=10). After 40 min perfusion with PES + OVA, the changes in water movement were less pronounced (24 [-3 to 43]) and neither KET nor GRA had any effect (KET 48 [28 to 87], GRA 41 [32 to 83]; NS). Na and Cl movement parallelled that of water .

Thus, the profound water secretion which occurs in the early stages of intestinal anaphylaxis is mediated by 5-HT_2 and 5-HT_3 pathways. Other mediators must also play an important role especially in the late phase of anaphylaxis.

F225

ELECTROGENIC ION TRANSPORT INDUCED IN VITRO BY BETHANECHOL ACROSS DISTAL COLON FROM FED, STARVED AND UNDERNOURISHED MICE HAS NEURAL AND NON NEURAL COMPONENTS.

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Electrogenic ion transport measured *in vitro* as the short-circuit current (Isc, μamps/cm^2 serosal area) across intact distal colon removed from fed, 48h starved and undernourished (4 days at 50% normal food intake) Swiss mice showed a biphasic response on serosal addition of the muscarinic agonist bethanechol (1mM). A transient decrease in the basal Isc, which returned to the baseline within 30 seconds, was followed by a large increase which plateaued at the maximum for at least 10 minutes. The starved colon had significantly greater negative and positive components compared to the fed and undernourished colons ($p<0.01$, unpaired t test). Serosal bethanechol acting on colons pretreated with 1 μM serosal tetrodotoxin (TTX) did not induce a significant decrease of the Isc in fed or starved colons while that in the undernourished was practically abolished. The maximal Isc increases induced by bethanechol were all reduced, especially in the fed ($p<0.01$) and starved colons ($p<0.001$) which also showed decay of their Isc after the maximum had been reached unlike the plateaus observed in the absence of TTX. Mucosal amiloride (0.1mM) had no effect on the biphasic responses of the Isc to bethanechol indicating that they did not involve changes in electrogenic Na^+ absorption. Pretreatment with mucosal diphenylamine-2-carboxylic acid (2.5 mM), a Cl^- channel blocker, surprisingly reduced, however, both the decrease and the increase in the Isc. Bethanechol thus activates electrogenic ion transport in fed and dietary-deprived distal colon by neural and non-neural mechanisms. The initial decrease in the basal Isc appears to be neurally mediated while the increase in Isc has both non-neural (direct action on colonocytes?) and neural components. The latter influences not only the maximum response but also its duration.

F226

IMPORTANCE OF MOLECULAR GEOMETRY ON PERMEATION RATES OF IN VIVO PERMEABILITY PROBES.

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It has been particularly difficult to explain why PEG 400 permeates the intestine 100 times more efficiently than lactulose and 51CrEDTA in vivo as these substances are all water soluble, of similar mol. wt. and chemically inert. One suggestion is that PEG polymers are elongated, as opposed to globular and therefore slip through small 'pores' which do not accommodate the other markers. We tested this by assessing permeation rates of 3-O-methyl-D-glucose (mol. wt. 194), D-xylose (150), L-rhamnose (164), lactulose (342), 51CrEDTA (340) and PEG (282-502) through a Visken dialysis membrane in an Ussing chamber. Incubations were hourly for 11 hours on 3 separate occasions. Permeation rates were calculated as conc (low side) / (high side) multiplied with the square root of the molecular weight so that if diffusion was unrestricted all markers would yield the same values (Grahms law). Results showed linear permeation rates over 11 hours. Permeation rates of monosaccharides were similar but more than twice that of the other markers. Five polymers of PEG were clearly separated but lactulose permeation rates were by comparison exactly as expected on the basis of mol. wt. Permeation rates of 51CrEDTA were significantly lower in all experiments presumably because of its negative charge at a pH 7. This shows that the membrane restricts diffusion according to mol. wt. and the results do not support the suggestion that the greater permeation rates of PEG 400 in vivo is due to an elongated structure.

F227

CALCIUM ABSORPTION AND BONE METABOLISM IN CROHN'S DISEASE (CD)

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Aim of this study was to investigate the occurrence of metabolic bone disease and its pathophysiology in selected patients with CD.
Methods: we investigated 14 male adults (age 25-50) with long-standing (over 5 years) ileal or ileo-cecal CD (n=5), or with ileal or ileo-cecal resection (n=9) for CD. All patients had no symptoms of bone disease and had an inactive CD (CDAI<150)), with no evidence of malabsorption.
The study was performed in late autumn and bone metabolism was investigated by measuring S-biochemical indicators (Alkaline phosphatase, Osteocalcin), minerals (Calcium, Phosphate, Magnesium) and relevant hormones (PTH, CT, 25-OH and 1,25-(OH)2vit.D, nephrogenic AMPc).
Calcium absorption was evaluated by means of 45Ca kinetics after an oral dose, and L2-L4 vertebral mineral density (BMD) was measured by Dual Energy X-ray Absorptiometry (Hologic QDR 1000).
Results: 7 patients (5 of whom resected) had a reduced Ca-intestinal absorption. Although a frank decrease of BMD was present only in 4 cases (Z score less than -2), 8 patients (57%) showed a BMD below 1 SD from normal mean (Z score less than -1).
No correlation between Calcium absorption and either vit.D metabolites or BMD was found.
S-biochemical tests were mostly normal.
Conclusions: 1. A high proportion (64%) of patients with inactive CD have reduced Ca absorption or low bone density without symptoms of bone disease. 2. The reduction of Calcium absorption seems to be independent of vit D metabolism. 3. These alterations may identify those patients who require treatment and should be suspected in asymptomatic cases with ileal or ileo-cecal CD or resection.

F228

CD4 LYMPHOCYTE COUNT AS A PREDICTOR OF THE CAUSE OF DIARRHOEA IN HIV-INFECTED INDIVIDUALS

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The CD4 lymphocyte count measured within 1 month of diagnosis was available in 382 HIV-seropositive individuals presenting with diarrhoea (more than 3 liquid motions/day). Of the 313 identified pathogens (cryptosporidium 99; microsporidium 21, giardia 22, Mycobacterium avium intracellulare (MAI) 37, Salmonella 36, Shigella 10, Campylobacter 44 and Cytomegalovirus (CMV) 44), 205 (65%) were found in patients with a CD4 lymphocyte of less than 50/mm^3. The relative frequency of different pathogens varied with the CD4 count: cryptosporidium was equally common in all groups; CMV colitis microsporidiosis and MAI infection only occurred in patients with a CD4 count of less than 200/mm^3 and the latter was significantly more common in patients with a CD4 count of less than 50/mm^3 ($p<0.001$). Multiple infections also occurred more often in this group. Patients with CD4 counts above 200 were significantly more likely to have no pathogen found despite extensive investigations ($p<0.001$). All the pathogens found in those with a CD4 count of more than 200 could be diagnosed on stool examination and blood culture alone but at least 21% of those in patients with a CD4 count of 50-200 and 25% in patients with a count of <50 require intestinal biopsy.
Conclusion: Duodenal and rectal biopsies are only required in the investigation of HIV-related diarrhoea if the CD4 count in <200/mm^3.

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SMALL INTESTINAL ABSORPTION OF MINERALS DURING ENTERAL FEEDING SUPPLEMENTED WITH SOY POLYSACCHARIDE FIBRE

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Fibre supplemented polymeric enteral diets are currently being prescribed widely in the UK. There is also evidence that mineral absorption may be adversely affected by the addition of fibre to the normal diet. As a result, the present study was carried out to quantitate and compare small intestinal absorption of the minerals Ca, Zn, Mg, Fe, Cu, and P during continuous intragastric infusion of:- 1) polymeric enteral diet (PD) (6.3gN/l; 1Kcal/ml), or 2) polymeric enteral diet (6.3gN/l; 1Kcal/ml), supplemented with a soy polysaccharide (20g/l) fibre source (PDSP). Thirteen normal subjects (PDSP n = 7, PD n = 6) were intubated with a multilumen tube, the distal end being positioned just proximal to the caecum. A 20 cm segment of terminal ileum was infused at 1ml/min with normal saline containing a non absorbable marker (0.5uCi/l H3-PEG), in order to quantitate steady state colonic inflows of minerals during continuous (7 h) intragastric infusion (82 mls/hr) of enteral diet. Total small intestinal absorption values (% of infused load ± SEM measured by flame photometry) for PD and PDSP respectively were; Ca 82.7 ± 2.18 vs 94.1 ± 1.09*; Zn 60 ± 9.14 vs 83.5 ± 4.6*; Mg 70.2 ± 2.77 vs 93.6 ± 1.85*; Fe 65.3 ± 5.2 vs 67.5 ± 6.3; Cu 48.9 ± 8.98 vs 62.7 ± 3.2; P 90.9 ± 3.6 vs 90.3 ± 3.05. (* - p< 0.05).

These data show that the addition of 20g/l soy polysaccharide to polymeric enteral diet has no adverse effect on the absorption of Fe,Cu or P but significantly increases the absorption of Ca, Zn, and Mg.

F231

ALTERATIONS IN ENZYME ACTIVITIES FOLLOWING CHRONIC LOW-FREQUENCY ELECTRICAL STIMULATION OF HUMAN GRACILIS MUSCLE

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Chronic low-frequency electrical stimulation (LFES) of fast-twitch, fatiguable skeletal muscle has been shown in experimental animals to result in transformation into a slow-twitch, fatigue-resistant muscle. This principle has been applied to the gracilis sling procedure for the treatment of patients with faecal incontinence in an attempt to achieve the fatigue-resistance appropriate for sphincteric function.

This study aimed to determine whether the metabolic activity of the human gracilis muscle may be modified by LFES.

Muscle biopsies were taken from 5 patients undergoing the gracilis neosphincter procedure before and after a period (7-16 weeks) of LFES (2-10 Hz). Succinate dehydrogenase (SDH) and lactate dehydrogenase (LDH) activities were assayed using a photometric technique. The resulte are expressed as the mean (SD) of 4 separate determinations on each biopsy.

	SDH µmolDCIP/min/mg prot		LDH µmol/NADH/min/mg prot	
Patient	Pre LFES	Post LFES	Pre LFES	Post LFES
1	1.49 (0.11)	1.79 (0.09)	0.60 (0.04)	0.64 (0.03)
2	0.09 (0.01)	0.51 (0.04)	0.26 (0.02)	0.27 (0.02)
3	0.73 (0.03)	1.10 (0.04)	0.67 (0.08)	0.48 (0.03)
4	0.29 (0.02)	0.32 (0.01)	0.70 (0.08)	0.81 (0.10)
5	0.67 (0.03)	0.86 (0.11)	0.66 (0.01)	0.56 (0.02)

These results indicate a significant increase (p=0.02, paired T test) in SDH activity but no significant overall change in LDH activity. This is consistent with a shift from predominantly anaerobic to aerobic metabolism, which would be expected to accompany an improvement in fatigue-resistance. The results also demonstrate the wide inter-patient variability in enzyme activities which has previously been reported.

This study demonstrates that the metabolic activity of the human gracilis muscle is modified by LFES.

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LONG TERM RESULTS OF POSTANAL REPAIR FOR IDIOPATHIC FAECAL INCONTINENCE.

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The short term results of postanal repair for idiopathic faecal incontinence are satisfactory but data on long term outcome is lacking. This study was carried out to document the short and long term results and to determine whether pre-operative tests predict outcome.

Method: 36 patients (33 F, mean age 57yrs) with idiopathic faecal incontinence were operated on by one surgeon between Sept 1985 and March 1991. Patients had resting (RP) and voluntary contraction (VCP) anal pressures and pudendal nerve terminal motor latencies (PNTML) measured pre-operatively. Symptoms were evaluated at 6 months after operation and again at a mean of 32 months (range, 6 - 72) in all 36 patients. Symptoms were classified as: Group A, no improvement or worse; Group B, minor improvement; Group C, marked improvement. 14 patients were available for post-operative physiology.

Results: At 6 months there were 6 (17%) patients in Group A, 12 (33%) in Group B and 18 (50%) in Group C. At final follow up there were 17 (47%) in Group A, 9 (25) in Group B and 10 (28%) in Group C. There were no significant differences in the pre-operative tests between the 3 groups at 6 months. Comparison of the pre-operative data in the final outcome groups showed (mean ± SEM): Group A vs Groups B & C; RP: 41 ± 12 cmH_2O vs 24 ± 8 (P=0.2), VCP: 12 ± 3 vs 27 ± 7 (P=0.07), PNTML 3.3 ± 0.44 mS vs 3.16 ± 0.4 (P = 0.8). Mean differences between post- and pre-operative results were: RP 39 ± 9 cmH_2O (P=0.09), VCP 26 ± 10 (P=0.22), PNTML -0.2 ± 0.5 mS (P=0.2). In 10 of the 14 patients tested the RP and VCP was increased postoperatively.

Conclusion: At 6 months 83% of patients had obtained some benefit from postanal repair but only 53% maintained this improvement with only 28% markedly better. There was a trend towards a more favourable outcome in patients with greater squeeze pressures pre-operatively but other tests were not of long term predictive value.

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DEMONSTRATION OF NEUROPEPTIDES IN THE INTERNAL ANAL SPHINCTER IN HEALTH AND FAECAL INCONTINENCE.

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Neuropeptides are important in control of intestinal motility and might play a central role in disease states. Little is known of their role in the normal internal anal sphincter (IAS) and whether abnormalities exist in incontinence.

Method: IAS from 16 women with IFI (mean age 58yrs, 26-83) undergoing post-anal repair and 12 cancer controls (age 61yrs, 51-74, 7F) were fixed in 4% paraformaldehyde. Cryostat sections (10µm) were incubated with primary antisera for 15 hrs. Rabbit antisera to vasoactive intestinal peptide (VIP), neuropeptide -Y (NPY), galanin, calcitonin -gene related peptide (CGRP), substance -P and peptide histidine isoleucine (PHI) were used. Sections were then incubated in goat-anti-rabbit fluorosceinisothiocyanate (FITC)-conjugated 2° anti-sera. Sections were examined with a Zeiss microscope equipped for viewing fluorescence.

Results: Tissues contained smooth muscle and some adjacent submucosa, but no longitudinal layer or myenteric plexus. Immunoreactivity was typically seen in nerve fibres between muscle bundles and in the submucosa. Generally the innervation was sparse with a greater density of innervation by VIP than of NPY or galanin, less PHI and very few CGRP or substance P-immunoreactive fibres. In sections from incontinent patients the distribution of peptides was the same and there was no significant difference in the amount of immunoreactivity.

Conclusion: There is no alteration in the density or distribution of neuropeptide immunoreactivity in idiopathic incontinence. In both controls and patients there is a greater density of VIP, NPY and galanin containing nerve fibres than PHI, CGRP or substance P-immunoreactive fibres.