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INTESTINAL GRANULOMOGENESIS IN ADULT VERSUS PRE-PUBESCENT *SCHISTOSOMA MANSONI*-INFECTED RHESUS MONKEYS.

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Many patients infected with the helminth *Schistosoma mansoni* suffer from gastrointestinal symptoms, including nausea and dysentery as well as hepatosplenomegaly. Epidemiological research has shown that there is a significant difference in the level of infection with this parasite between children and adults. This age-related difference is possibly due to a shift in susceptibility to infection. To investigate these age-related changes in *S. mansoni*-induced enteric granulomogenesis, pre-pubescent and adult rhesus monkeys (*Macaca mulatta*) were infected for 8 weeks with *S. mansoni*. Marked colonic granuloma formation was present in both pre-pubescent and adult monkeys often showing a diffuse pancolitis. On histopathological and immunohistochemical grounds, two distinct types of granulomas could be discerned: classic -type "C" , resembling the granulomas seen in *S. mansoni* infected rodents, and foreign body type "FB" granulomas. The total number of granulomas in pre-pubescent animals was significantly increased. When divided by subtype, there were significantly more "FB" granulomas in pre-pubescent animals than in adult animals. No difference was seen in granuloma volume between the two age groups. Pharmacological in vitro testing did not demonstrate a significant difference in colonic contractility between the two groups of infected animals. The morphological results could be explained by a higher level of susceptibility to infection in the younger age group. From previous studies the "FB"-granuloma type is known to follow the "C"-granuloma in time and thus presents a later stage in the granulomatous process, suggesting a faster immune response in younger animals. In summary, in this study data are presented suggesting a distinct, age-related intestinal granulomatous reaction pattern towards entrapped *S. mansoni* eggs. No evidence was found whether this difference in immune response had functional implications on the intestinal neuromuscular function at the acute stage of infection.

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FECAL LACTOFERRIN AS AN INDICATOR OF DISEASE ACTIVITY IN INFLAMMATORY BOWEL DISEASE (IBD).

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Background: Inflammatory Bowel Disease (IBD) is characterized by a chronic immune-mediated inflammatory response that results in histologic damage of the intestinal lining. Numbers of immune cells, such as neutrophils, are markedly increased in the inflamed mucosa. Lactoferrin is a granule component of neutrophils and fecal lactoferrin excretion might be a useful marker for disease activity in inflammatory bowel disease. Objectives: In this study, we determined the levels of fecal lactoferrin in healthy controls to subjects with either ulcerative colitis or Crohn's disease. Lactoferrin levels were compared to disease activity. Method: Fecal lactoferrin concentrations were determined using a polyclonal antibody based-enzyme-linked immunoassay (*LEUKO*-ELISA, TechLab, Inc.). Lactoferrin levels were reported as μg/g wet weight (wt) of feces. Disease activities were assessed based on symptoms and endoscopy examinations. The study included 91 fecal specimens from the following groups of subjects: healthy controls (59), ulcerative colitis (8) and Crohn's disease (24). Results: Lactoferrin levels ranged from 0.01 to 14.55 μg/g wet wt for healthy controls, 0.18 to 1022.56 μg/g wet wt for subjects with ulcerative colitis and 0.10 to 279.60 μg/g wet wt for subjects with Crohn's disease. A comparison between disease activity and lactoferrin levels showed 100% (11/11) of persons with active disease had levels $\geq$ 10.00 μg/g wet wt, 76.1% (16/21) of individuals with inactive disease showed levels $\leq$ 15.02 μg/g wet wt and 96.6% (57/59) of the healthy controls had levels of $\leq$ 8.15 μg/g wet wt. Active and inactive disease groups were significantly different from each other and the healthy controls ($p<0.05$). Conclusions: Our results show that fecal lactoferrin correlates with active IBD. These findings suggest that lactoferrin may be useful for determining the effectiveness of drug therapy in patients with IBD. Further analysis will be done to compare the lactoferrin levels between ulcerative colitis and Crohn's disease.

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EFFECT OF THE ENKEPHALINASE INHIBITOR, RACECADOTRIL, ON INTESTINAL 5-HYDROXYTRYPTAMINE (5-HT) AND FLUID TRANSPORT IN CHOLERA TOXIN INDUCED SECRETION.

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Aims: 5-HT is known to be a mediator of cholera toxin-induced secretory diarrhoea. Racecadotril, an enkephalinase inhibitor, has been shown to inhibit cholera toxin (CT)-induced secretion in a human perfusion model. We aimed to determine whether racecadotril inhibits intestinal secretion via a 5-HT dependent or independent pathway. Methods: Male Wistar rats were starved for 24h with free access to water, and anaesthetised with sodium pentobarbitone (60mg/kg) prior to isolation of a 20cm segment of jejunum between proximal and distal cannulae. Racecadotril (10mg/kg) or vehicle was administered via the tail vein 30min prior to instillation of CT (50μg in 2ml normal saline) into the segment. After 2h incubation with CT, perfusion of the segment was performed with ^{14}C-labelled polyethylene glycol solution at 30ml/h for 30 min to establish a steady state of secretion. Three 20 min collections of perfusate were made for assessment of fluid flux by scintillation counting. Three 2min aliquots were collected into 10% perchloric acid and immediately frozed at -70°C for analysis of 5-HT by high performance liquid chromatography with fluorimetric detection. Results were analysed by Mann Whitney analysis and the level of significance was set at $p\leq0.05$ with data quoted as median (interquartile range). Results: Racecadotril (R) significantly reduced CT-induced secretion (indicated by negative value) compared with vehicle (V). (V n=9 -25.8 (7.75 to -47.5)μl/g/min) versus R n=9 -17.9 (-9.25 to -34.75) μg/min p=0.001). 5-HT data was available for R n=6 and V n=5. When equivalent data was assessed secretion results for R n=6 (-14.6(-3.7 to -32.9) μ1/g/min) versusV n=5 (-43.3 (-27.4 to -53.55) μl/g/min) were different (p=0.05) but 5-HT levels were unchanged (R 6.6pmol/mg/dry weight tissue/h (6.85-5.8) vs V 4.13 (6.41-3.8) p=0.25). Conclusion: These results indicate that intravenous racecadotril inhibits CT induced secretion, although luminal 5-HT concentrations were unchanged. This implies that enkephalinase inhibition has its effects via a pathway indpendent of any effects on 5-HT release and must act after 5-HT has had its effects on secretion. This supports the hypothesis that the enteric nervous system contains inhibitory (pro-absorptive) synapses following the site of action of 5-HT in the secretory cascade.

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DECREASED CONCENTRATIONS OF SACCHARASE-ISOMALTASE AND VILLIN IN INTESTINAL EPITHELIAL CELLS OF CROHN'S DISEASE AND ULCERATIVE COLITIS.

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Introduction In intestinal epithelial cells a defect in the apical membrane could allow an increased intestinal uptake of luminal antigens and thus contribute to the pathogenesis of Crohn's disease (CD) and ulcerative colitis (UC). The aim of our study was therefore to analyse the labelling density of the microvillus proteins saccharase-isomaltase (SI) as a membrane protein and villin (V) as a cytoskeleton protein in morphologically normal enterocytes (NE) and enterocytes characterized by rapid antigen uptake into the cytosol (RACE) and by ultrastructural alterations described in Int J Colorectal Dis 14: 41-6; 1999). Methods The microvillus labelling density (LD) of immunogold binding to antibodies against SI and V was determined by immunoelectron microscopy for an area of 50 μm^2 in NE and RACE of CD (n=5), UC (n=5) and normal controls (NC, n=5). 20 NE and 20 RACE per specimen were analysed. Wilcoxon U-test was used for statistical analysis with $p < 0.05$ considered to be significant. Results Labelling density of both SI and V in NE (*$p<0.01$) and RACE (**$p<0.01$) were significantly decreased in both CD and UC compared to NC. Conclusion The suggested increase of intestinal permeability can be explained by the observed decrease in key membrane proteins of intestinal epithelial cells in CD and UC.

Labelling density for SI and V in NE and RACE of CD, UC and NC

	CD NE	CD RACE	UC NE	UC RACE	NC NE	NC RACE
SI [LD; particles per μm^2]	41±11*	21±8**	47±7*	15±6**	58±6	35±8
V [LD; particles per μm^2]	22±5*	7±3**	19±5*	9±4**	25±4	15±6

± standard deviation of the mean