●608 DIRECT AND INDIRECT MECHANISMS FOR REGULATION OF HUMAN HEPATIC ACUTE PHASE GENE EXPRESSION

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Several distinct and well-characterized cytokines can mediate fever and changes in metabolism characteristic of the host response to inflammation/injury. In this study, the cytokines interleukin-1 (IL-1), cachectin/tumor necrosis factor (TNF) and interferon-γ (IFNγ), acting on human hepatoma cells (HepG2,Hep3B), directly mediated changes in expression of several plasma proteins, characteristic of the acute phase response. Recombinant human IL-1β or TNFα increased steady state levels of mRNA for and rate of synthesis of complement proteins C3, factor B, α-1-antichymotrypsin and decreased steady state levels of mRNA for and rate of synthesis of albumin and transferrin in HepG2 and Hep3B cells. Recombinant human IFNγ increased steady state levels of mRNA for and rate of synthesis of IL-1- and TNF-unresponsive complement protein C4. Recombinant human IL-2 also elicited hepatic acute phase gene expression but through an indirect pathway involving the induction of monocyte IL-1 release. The effect of these cytokines on hepatic acute phase genes (factor B, C4) was also evident in mouse fibroblasts transfected with the cloned human factor B or C4 genes suggesting the presence of regulatory elements within the gene or its flanking regions. These results indicate that the human hepatic acute phase response can be studied in a human hepatoma cell with the use of well-characterized and highly purified cytokines. In vivo, hepatic acute phase gene expression is likely to involve several different mediators acting through several pathways.

●609 CYCLIC AMP SUPPRESSES COLLAGEN SYNTHESIS BY HUMAN INTESTINAL SMOOTH MUSCLE (HISM) CELLS.

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HISM cell collagen production appears to play a major role in the pathogenesis of intestinal strictures in Crohn's disease. HISM cells in culture produce large amounts of collagen in the presence of fetal bovine serum (FBS). To determine the role of cAMP in the regulation of this collagen production, HISM cells were isolated from normal human jejunum, grown in culture and exposed to cholera toxin (CT, 10 ng/ml), isobutylmethylxanthine (IBMX, 0.16 mM) and CT + IBMX for 48 hours. Collagen synthesis was determined by the incorporation of ^{3}H proline into collagenase-sensitive protein. CT and IBMX caused significant reductions in collagen synthesis and non-collagen protein synthesis (NCP). The inhibitory effects of CT and IBMX alone were selective for collagen as evidenced by significant reductions in relative collagen synthesis (RCS).

Condition	Collagen(cpm/ng DNA)	NCP(cpm/ngDNA)	RCS
Control	753±135	3408±135	3.5±.3
CT	*240±41	*2092±124	*2.1±.4
IBMX	*181±6	*1220±65	*2.7±.1
CT + IBMX	*222±9	*1117±36	3.5±.2

(means, n = 4, * significantly different from controls, $p < .05$)

CT, IBMX and CT + IBMX caused a 3.5, 3 and 33 fold increase in HISM cell cAMP levels respectively. Increased cAMP levels down-regulate collagen synthesis by HISM cells. This response is most selective for collagen synthesis with smaller elevations in cAMP. Supported by NIH grants AM07718, AM34151 and the N.F.I.C.

† 610 HEMOLYSIS DURING SULFASALAZINE (S) THERAPY FOR PEDIATRIC INFLAMMATORY BOWEL DISEASE.

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Adverse hematologic reactions to S therapy have been well-documented in isolated IBD patients. In prior reports, hemolysis has been noted to be infrequent, and has occurred within 2-4 weeks of initiation of therapy or coincident with an increase in dosage. Most have been receiving generally high dosages (>4g/day). These toxic manifestations are generally believed to be associated with a slow-acetylator phenotype. After diagnosing three individuals with S-induced hemolytic anemia occurring from 2 to 30 months after the initiation of therapy, we undertook to study the prevalence of S-induced hemolysis in a group of IBD patients (3-19 y.o.) without evidence of active GI blood loss. Out of 20 patients (15 U.C., 5 Crohn's), nine (45%) exhibited evidence of hemolysis by reticulocyte count (average 6.9%, range 2.4-12.8%) and haptoglobin level (average 10 mg/dl, range 0-30, nl 100-300 mg/dl). The average dosage was only 50 mg/kg/day S with a maximum of 3g/day. Upon cessation of S, hemolysis promptly resolved and the hemoglobin level increased an average of 2.1g/d. Prior observation of this hemolysis was obscured by the common occurrence of anemia and reticulocytosis in IBD, and by the laboratory variability in measurement of reticulocyte count.

We conclude that in pediatric IBD patients S-induced hemolysis is common, often late in onset, and occurs with modest dosages. Patients on S-therapy should be followed with routine reticulocyte counts and haptoglobin levels as long as therapy persists.

† 611 SERUM α_1-ANTITRYPSIN (α_1-AT) LEVELS AS A MARKER OF ACTIVITY IN INFLAMMATORY BOWEL DISEASE (IBD).

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A number of investigators have assessed the activity of IBD through the fecal clearance of α_1-AT. α_1-AT is a serine protease inhibitor present in the α_1-globulin fraction of blood. In our investigations in IBD, we have found that the simple and rapid determination of serum α_1-AT alone gave a useful measure of disease activity. We compared the sensitivity and specificity of serum α_1-AT levels versus ESR's in 1) the initial diagnosis of IBD and 2) the evaluation of disease activity in patients with known IBD. Serum α_1-AT was measured by radial immunodiffusion (elevated >350 ug/dl), and ESR by the Westergren method (elevated >20 mm/hr). Diagnosis and disease activity was determined by accepted clinical, endoscopic, radiologic, and histologic methods.

	(1) diagnosis-IBD vs non-IBD		(2) active vs inactive	
	sensitivity	specificity	sensitivity	specificity
α_1-AT	14/15 (93%)	11/12 (92%)	48/49 (98%)	28/29 (97%)
ESR	8/15 (53%)	12/12 (100%)	29/49 (59%)	29/29(100%)

For the initial presentation (1), α_1-AT was elevated in 93% of patients vs 53% with elevated ESR. Both tests were relatively specific (92% vs 100%) for patients without IBD. In the evaluation of disease activity, α_1-AT was elevated 98% of the time vs 59% for ESR during active disease. Both were normal in inactive disease. Analysis with respect to sex or IBD-type (U.C. vs Crohn's) yielded similar findings. Conclusions: Serum α_1-AT is a better indicator of IBD activity than the commonly used ESR. We suggest that α_1-AT determination be used both in the diagnosis and follow-up of patients with IBD.

▲612 CLINICAL BENEFITS OF CO-INFUSING A LIPID EMULSION WITH AMINO ACIDS-DEXTROSE SOLUTIONS IN NEWBORN INFANTS.

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Metabolic consequences of infusing lipids have been widely investigated. We evaluated the local effects of varying the proportions of parenteral glucose and fat on the venous tolerance or patency of infusion sites. Thirty-two observations were made in 16 infants; (X̄±SEM, birthweight:2.15±0.1 kg, gestational age: 34±1 wk). In a paired cross over design the patients received for a given level of energy (60 vs 80 kcal/kg/d), two 6 day isocaloric and isonitrogenous (434±3.4 mg/kg/d,n=32) regimens differing only by the fat intake (LIP-1: 1.03±0.02, LIP-3: 2.78±0.05 g/kg/d). Minutes between changes in infusion sites (T), and osmolarity of the mixtures (Osm, mOsm/l) were compared between each treatment.

	60 kcal/kg/d (n=8)		80 kcal/kg/d (n=8)	
	Osm	T	Osm	T
LIP-1	702±16	803±110	784±13	921±114
LIP-3	547±16	1542±227	702±8	1242±130
p	<0.001	<0.05	<0.001	= 0.054

These data show that the lipid emulsion significantly reduces the final osmolarity of the mixture and thereby increases the patency of the infusion sites. Moreover, for a same osmolarity and glucose intake, the addition of lipids (60 kcal LIP-1 vs 80 kcal LIP-3) increases the infusion time significantly ($p<0.05$). Whether biochemical or physical, this protective effect of the lipid emulsion demonstrates that the quality of fuel mixtures has an important role on the patient's comfort.

613 PREVALENCE OF COELIAC DISEASE IN TWO DIFFERENT ETHNIC GROUPS.

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The expression of coeliac disease is assumed to be influenced by both genetic and environmental factors. The aim of our study was to investigate the prevalence and HLA-type in two different ethnic groups, a German and an Italian living in South Tirol. Those two groups have very rarely intermarried. The live birth rate during the time period 1973-82 (ten years) was 42,739 for the German group and 14,874 for the Italian group. Fifty new cases of coeliac disease, born during this period, were diagnosed according to the ESPGAN-criteria, 45 were German and 5 Italian. The prevalence in the German group was 105/100.000, and 33/100.000 in the Italian group. HLA-typing was performed in 40 patients and in 50 German and 50 Italian controls. Forty-three percent of the CD patients were positive for B8, 85% for DR3, 66% for DR7 and 56% for DR3/7. No difference in the expression of HLA B8, DR3, DR7 was found in the Italian and German controls. Seventeen percent in both control groups were positive for HLA B8, 35% for HLA DR3 and 30% for HLA DR7

Conclusions: The prevalence of the disease in two ethnic groups living under similar environmental conditions was significantly different. The data presented here strongly suggests that there is no association between the prevalence of the disease and HLA-type in this population study. Further from preliminary data it may be postulated that the age of introduciton of gluten to the infant diet may affect the prevalence of coeliac disease.