

Falk Symposium

176



Environment and Lifestyle – Effects on Disorders of the Digestive Tract

October 9 – 10, 2010
Freiburg, Germany



Abstracts
Poster Abstracts

**Abstracts of Invited Lectures
Poster Abstracts**

Falk Symposium 176

IV Falk Gastro-Conference

**ENVIRONMENT AND LIFESTYLE – EFFECTS ON DISORDERS
OF THE DIGESTIVE TRACT**



Freiburg (Germany)
October 9 – 10, 2010

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Session I

Genetic basis of digestive diseases

Genetic susceptibility for disorders of the digestive tract – Principles

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Multiple common gastrointestinal disorders are thought to have complex etiologies that involve interactions between host genes and environmental factors. Disease gene mapping by genetic linkage analysis in families has successfully led to the identification of low frequency, high penetrance risk alleles responsible for Mendelian traits and also some higher penetrance risk alleles in complex traits (e.g., *CFTR* risk alleles in cystic fibrosis, *IL10RA* and *IL10RB* risk alleles in early onset IBD, *NOD2* risk alleles in Crohn's disease). However, the genetic linkage mapping approach has limited power to detect loci with only modest effects such as those that are thought to be responsible for much of the heritability of common, complex traits. Genetic association mapping in populations has greater power to detect loci with modest effects than genetic linkage mapping in families. In recent years, an explosion of genome-wide association studies (GWAS) has been enabled by the Human Genome Project, The International HapMap Project, and technological advances that made rapid and cost-effective analysis of genetic differences between cases and unaffected controls possible. Gastrointestinal disorders in which GWAS have been published include colorectal cancer, celiac disease, Crohn's disease, eosinophilic esophagitis, esophageal cancer, hepatitis B, hepatitis C, Hirschsprung's disease, pancreatic cancer, primary biliary cirrhosis, primary sclerosing cholangitis, and ulcerative colitis. GWAS in the inflammatory bowel diseases, Crohn's disease and ulcerative colitis, have been among the most successful for any complex traits. They have provided valuable clues about the involvement of specific biological pathways in inflammatory bowel disease pathogenesis (e.g., Th17 pathway in both Crohn's disease and ulcerative colitis, autophagy in Crohn's disease, mucosal barrier integrity in ulcerative colitis). Several of the inflammatory bowel disease loci appear to be shared with other immune-mediated, chronic inflammatory disorders, such as asthma, celiac disease, multiple sclerosis, psoriasis, type I diabetes mellitus and systemic lupus erythematosus. Other lessons from the inflammatory bowel disease GWAS include: 1) many of the association signal peaks are located outside known gene coding regions, 2) several of the risk loci appear to play a role in transcriptional regulation based on expression quantitative trait loci (eQTL) evidence, and 3) most of the identified risk alleles have modest effect sizes and much of the heritability remains unexplained. Ongoing approaches to finding the missing heritability include additional replication studies that delve deeper into lists of GWAS meta-analysis hits in large study samples, dense genotyping of many additional known genetic variants within established risk loci, resequencing within established risk loci to identify low frequency risk variants, additional GWAS to fill in gaps in the coverage of common human genetic variation, and studies of unique families that may carry rare disease-causing genetic variants. Functional studies to understand the biological relevance and environmental interactions of established risk loci will be of crucial importance.

Epigenetics – Principles and effects

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Epigenetics is defined as heritable changes in gene expression that are, unlike mutations, not attributable to alterations in the sequence of DNA. Two predominant epigenetic mechanisms are DNA methylation and histone modification. Epigenetic regulation of gene expression appears to have long-term effects and wide ranging effects on health. Diet and environmental exposures may potentially alter the level and scope of epigenetic regulation, thus, interesting developments in the study of epigenetics might explain the correlations the researchers have found between lifestyle and risk of disease.

Abnormal methylation patterns have been linked to a number of digestive diseases including Barrett's esophagus, cirrhosis, inflammatory bowel disease, and numerous gastrointestinal malignancies. DNA methylation refers to the addition or subtraction of a methyl group to a cytosine residue in a sequence of DNA. This methylation is controlled by DNA methyltransferase (DNMT) enzymes. Global (*i.e.*, genome-wide) decreases in methylation, or *hypomethylation*, are most functionally relevant when they occur in coding regions of genes, leading to alternative versions or levels of messenger RNA. It is theorized that hypomethylation contributes to diseases and carcinogenesis by favoring mitotic recombination, leading to deletions, translocations, and chromosomal rearrangements. The addition of methyl groups, or *hypermethylation*, is much more gene-specific. Regions of the genome that are rich in the sequence of a cytosine preceding a guanine (CpG dinucleotide) are known as CpG islands. In particular, CpG islands exist in the promoter regions of approximately half of all genes. Hypermethylation of CpG islands in the promoter region of a gene may result in its transcriptional silencing and loss of protein expression. Thus, hypermethylation of certain genes is now recognized as a means of silencing alternative to mutation or allelic loss in the development of diseases and cancer. The impact of carcinogens, diet (*e.g.*, folate), or other environmental factors on the level of methylation remains to be elucidated and is an area of active research.

Histones are the protein components of chromatin, the structure around which DNA is wound. Histones also participate in the regulation of gene expression. There are several types of post-translational modifications that can affect histones, including methylation, acetylation, phosphorylation and ubiquitination. These modifications can affect interactions between DNA and histones, leading to alterations in gene transcription, DNA repair, DNA replication and even the organization of chromosomes. The full spectrum of histone modifications and all their combinations form a remarkably complex network of genetic regulation. Modifications can occur in different histone proteins, residues and variants. Alterations can involve different chemical structures, such as acetyl groups, methyl groups and phosphate ions. Histones can be mono-, di- or trimethylated. In general, histone acetylation is associated with transcriptional activation, and deacetylation is linked with transcriptional repression. Thus, deacetylation is implicated in the silencing of tumor suppressor genes in carcinogenesis. The effect of histone methylation depends on

the amino acid affected, and the amino acid location in the histone tail. Further complexity is observed when hypermethylation and histone modification work in concert to alter gene transcription.

In summary, epigenetic phenomena have emerged as a fundamental pathway in the pathogenesis of numerous diseases. Disorders of the digestive system are no exception: in fact, many exciting discoveries about epigenetics in general have been made by studying diseases of the gastrointestinal tract and hepatobiliary tree. Epigenetic modifications of DNA in cancer and precancerous lesions offer hope and the promise of novel biomarkers for early cancer detection, prediction, prognosis, and response to treatment. Furthermore, reversal of epigenetic changes represents a potential target of novel therapeutic strategies and medication design. The beauty of epigenetic modifications to DNA is that they are potentially preventable or reversible. In the future, it is anticipated that innovative diagnostic tests, treatment regimens, and even lifestyle modifications will be based on epigenetic mechanisms and be incorporated into the gastroenterologist's practice.

Interactions between genetic susceptibility and environment: Examples from the GI tract

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During the last few years significant advance has been achieved in the understanding of the pathogenesis of inflammatory bowel disease (IBD). From twin studies it was evident that there more than 50% concordance of CD in monozygotic twin pairs¹⁻². A recent study again has shown concordance for CD in 63.6% among monozygotic twins, however, only 3.6% among dizygotic twins³. These data showed that the genetic background is responsible for at 50% of the risk or “susceptibility” to develop CD. Obviously it is not a sufficient condition as otherwise there would be 100% concordance of disease in monozygotic twin pairs. Environmental factors as well must play an important role. This is further supported by the fact that there is only slow development in genetic risk factors over thousands of years. In contrast the incidence of CD and UC has dramatically increased in Western countries in the last 100 years. This further supports the concept of a “Western lifestyle factor(s)” that triggers chronic intestinal inflammation in a genetically susceptible host.

The proof of the concept of a genetic susceptibility was achieved in 2001 with the discovery that NOD2/CARD15 is the most important susceptibility gene for CD⁴⁻⁶. The function of NOD2 has been investigated in detail. The most important information may be that it is an intracellular “alarm button”, a receptor recognizing invading bacteria, that entered the mucosal wall. Muramyl dipeptide (MurNAc-L-Ala-D-isoGln, MDP), a component of the bacterial wall derived from peptidoglycan as the essential structure in bacteria, was found to be the major ligand for NOD2⁷⁻⁸. MDP is a component of the wall of Gram-positive bacteria. NOD2 mutants associated with susceptibility to CD seem to be deficient in their recognition of MDP⁸. Interestingly, MDP was long known to be the essential structure in Freund’s adjuvans important for vaccination. In a genome-wide association study a disease association was found in the autophagy-related 16-like 1 gene (ATG16L1) which could be replicated⁹⁻¹⁰. The ATG16L1 gene encodes a protein in the autophagosome pathway that processes intracellular bacteria.

CD is now also discussed as an impaired and inadequate immune reaction to the gut bacteria which are a part of our environment (or perhaps “in-vironment”). In addition to NOD2 there are more “innate” pathways by which commensal and pathogenic bacteria can directly interact with cells of the intestinal mucosa. The “environment-concept” and the “genetic concept” of IBD pathophysiology are converging.

With the finding, that most susceptibility genes for CD and UC are involved in innate immune mechanisms and the primary defense against bacteria entering the mucosa, for the first time a unifying concept of the “genetic pathophysiology hypothesis” and the “environment pathophysiology hypothesis” of IBD was possible. Bacteria are the link between environment and mucosal defense system.

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Session II

Mechanisms of environmental effects I

Hygiene and other early childhood influences

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The current “Darwinian” synthesis of the Hygiene Hypothesis, better named the “Old Friends” hypothesis, suggests that the increase in chronic inflammatory disorders that started in Europe in the mid-19th century and progressed until the late 20th century, is at least *partly* attributable to immunodysregulation resulting from lack of exposure to microorganisms that were tasked by co-evolutionary processes with establishing the “normal” background levels of immunoregulation. This presentation will discuss the following propositions.

The essential role of these organisms is an example of “evolved dependence”. The relevant organisms co-evolved with mammals, already accompanied early hominids in the Paleolithic and are associated with animals, mud and faeces. These organisms often establish stable carrier states, or are encountered continuously in primitive environments as “pseudocommensals” from mud and water. These organisms were **not** lost during the 1st epidemiological transition, which might even have resulted in increased exposure to them. On the other hand, the crucial organisms are lost progressively as populations undergo the 2nd epidemiological transition (modern urban environment). Recently evolved sporadic “childhood infections” are not likely to have evolved immunoregulatory roles, and epidemiology supports this contention. The consequences of the loss of the “Old Friends” are aggravated by other modern environmental changes that also lead to enhanced inflammatory responses (obesity, vitamin D deficiency, pollution (dioxins) etc). The range of chronic inflammatory disorders that is affected is larger than had been assumed (allergies, autoimmunity, inflammatory bowel disease, *but also* celiac disease, food allergy, vascular disease, some cancers, depression/anxiety (when accompanied by raised inflammatory cytokines)).

Nutritional influences

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Nutritional factors, as a source of luminal antigens, have been thought to be an important factor in the immunopathogenesis of numerous gastrointestinal diseases. In some diseases, the role of the nutritional component is causal in the susceptible host. Such diseases include celiac disease, a common heritable chronic inflammatory condition of the small intestine induced by dietary wheat, rye and barley, in susceptible individuals. Specific *HLA-DQA1* and *HLA-DQB1* risk alleles are necessary, but not sufficient, for disease development. The well-defined role of HLA-DQ heterodimers encoded by these alleles is to present cereal peptides to CD4+ T cells, activating an inflammatory immune response in the intestine. Genome-wide association studies (GWAS) have been performed, which identified the *IL2-IL21* risk locus and other genes with immune functions and key roles in thymic T-cell selection. Another example for this group is Wilson's disease, an autosomal recessive disorder of copper metabolism caused by mutation of the *ATP7B* gene, resulting in a defect of biliary copper excretion and toxic accumulation in the body, especially in the liver, brain and cornea, resulting in hepatic and/or neurological symptoms.

In other diseases, however, the association is less well established. In such endeavor, epidemiological observations may become a valuable part of the overall investigations aimed at identifying dietary factors, which are involved in the initiation and perpetuation of the specific disease. As an example, relationships between nutrition and colorectal cancer have been early hypothesized (e. g. folate, calcium, vitamin D, red meat). Similarly, intake of certain diet constituents like fat, refined sugar, fruits, vegetables and fibre was reported to be associated with the expression of inflammatory bowel diseases. In addition, in children with active Crohn's disease, enteral nutrition was found to be equally effective as corticosteroids in induction of remission, with mucosal healing induced by downregulation of mucosal pro-inflammatory cytokine profiles in both the ileum and the colon after enteral nutrition. However, the particular effect of the consumption of each type of food remains questionable in most cases, at least in part because of insufficient data and serious methodological limitations (e. g. recall bias, heterogeneity between collected data, lack of correction for covariates, difficulties in double blinding).

The role of physical activity and obesity on GI disease

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There has been an epidemic of obesity in the Western world. A “normal” body mass index (BMI) is no longer the norm in the US with two thirds of adults categorized as overweight or obese (1). The reasons for this are multifactorial but, in part, relate to an increasingly sedentary lifestyle with the ascendancy of the car and television. Obesity and lack of physical exercise represents a major public health problem and the next US generation may be the first to show a decline in life expectancy in over two centuries. This lecture will outline the epidemiological evidence for the effect this will have on GI disorders.

Obesity increases overall cancer risk and GI cancers are well represented in this list. BMI is associated with an increased risk of esophageal adenocarcinoma, gastric, gallbladder, pancreatic and colorectal cancer (2). There are several plausible biological mechanisms that could explain these associations. Individuals that are overweight tend to eat less fruit and vegetables which may protect against a variety of cancers. Obesity is a key underlying factor in the etiology of the metabolic syndrome characterized by obesity, insulin resistance, hyperinsulinemia and dyslipidemia (3). Insulin increases free insulin like growth factor (IGF-I) levels, which can promote cell proliferation (4). Diabetes mellitus is associated with an increase risk of colorectal cancer (5) and the Nurses Health study found that the relative risk of colorectal cancer increased with increasing IGF-I levels (6). Adipose tissue is an endocrine organ that produces a number of proteins including the adipokines leptin, adiponectin, resistin, and visfatin, as well as cytokines such as TNF-alpha, and IL-6 (7). The production of proinflammatory cytokines may cause a chronic inflammatory response that is recognized as an important factor in carcinogenesis. Some adipokines may have direct effects on the carcinogenic process with adiponectin selectively inhibiting several mitogenic growth factors. Low adiponectin levels that are found in obese subjects may therefore promote cell proliferation and carcinogenesis (8).

Obesity is also a risk factor for gastrointestinal disorders other than cancer. There is a consistent association between obesity and gastroesophageal reflux disease and this may also explain the association between BMI and esophageal adenocarcinoma. Body mass index and waist hip ratio are both independent predictors of gallstone development (9) and it is possible that increased hepatic secretion of cholesterol and may lead to an increase propensity to cholesterol rich gallstones.

Obesity may be a risk factor for severity of acute pancreatitis and is associated with increased mortality according to a systematic review of five randomized controlled trials (10). The mortality findings rely heavily on the one randomized trial (60) although the concept is biologically plausible if adipose tissue is considered an endocrine organ secreting predominantly proinflammatory adipokines.

There have been four studies (11) that have assessed the relationship between adiposity and gastrointestinal symptoms. All reported a positive association between BMI and diarrhea (11) and two studies also found an increased risk of vomiting and upper abdominal pain (11). The reason for this association is unclear. It may relate to residual confounding factors as two of these studies adjusted for only age and gender (11). The symptoms may also be a direct result of size of meal ingested.

Large meals will lead to rapid gastric distention, which may lead to an increase risk of vomiting. Alternatively, in those with normal or increased gastric emptying, there will be a rapid osmotic bolus delivered to the small bowel that cannot be handled normally. The adipokines released in obesity may also have direct endocrine effects that may impact on the motility of the gastrointestinal tract (12). Functional gastrointestinal disorders are hypothesized to be a result of an initial inflammatory insult to the gastrointestinal tract that modifies visceral sensitivity and/or motility (13). Obesity may therefore increase the risk of functional gastrointestinal disorders due to the release of proinflammatory cytokines.

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Session III

Mechanisms of environmental effects II

Infections as trigger for chronic gastrointestinal disorders

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Apart from acute intestinal diseases (infections) which are often self limited (gastritis, enteritis, colitis), some pathogenic microorganisms may also lead to chronic gastrointestinal diseases.

I will discuss clinical situations in which the persistence of microorganisms induces or perpetuates chronic inflammatory diseases, and degrees of reversible or irreversible proliferation of various cells in the gastrointestinal tract (the extreme being adenocarcinoma and lymphoma).

1. Chronic gastrointestinal inflammatory or tumoral diseases with a clearly established microbial origin

The best example is certainly *Helicobacter pylori*, which is involved in the pathogenesis of acute gastritis, chronic gastritis, ulcers, lymphoma and gastric adenocarcinoma. Major lessons have been – the time for doctors to accept the role of *H. pylori* in the pathogenesis of each of the gastric diseases. – the difficulty to eradicate a microbe from its niche – variability of the risk depending on the strain of *H. pylori* and on hosts – the role of a microbe as carcinogen and the fact that the microbe may have disappeared at the (late) time of cancer.

It took also a long time to establish the pathogenic role of *Clostridium difficile*. Before the demonstration of the role of its toxins in the genesis of symptoms and colonic lesions, clinicians attributed pseudomembranous colitis to *Staphylococcus aureus*, since this microorganism was often isolated from the stools of the same diseased patients. The lesson for clinicians is that it is important to be aware of the wide ecological implications of antibiotic-induced disorders and not to focus only on the isolated results of some microorganisms.

I will also summarise the discoveries of the roles of *Tropheryma whipplei* and that of *Campylobacter jejuni* in Whipple disease, and alpha chain disease respectively. These demonstrated perfectly the progresses allowed by molecular microbiology and the role of microbes in lymphoproliferative disorders.

2. Inflammatory bowel disease (IBD)

Opportunistic pathogens are detected in the stools or mucosa of certain subjects with Crohn's disease more often than in healthy subjects (although inconsistently). They include *Mycobacterium avium paratuberculosis*, adherent-invasive *Escherichia coli* (AIEC) or *C. difficile*. I will discuss their potential role in onset and perpetuation of inflammation but also the hypothesis for their frequent presence in patients (constitutive defects in defensins and dysbiosis with defects of protective firmicutes). A dysbiosis has been repeatedly observed in patients with IBD, both in faecal samples and in the mucosa associated microbiota.

3. Perspectives

New tools to detect the presence of microbes, microbial signals, molecules or by-products open fantastic opportunities for discoveries. I will briefly summarise what can be expected from metagenomics, metatranscriptomics and metabolomics of the gastrointestinal ecosystems. Major tracks for the present research concern irritable bowel syndrome, the role of small bowel bacterial overgrowth in intestinal and liver diseases], colon cancer and obesity.

Mechanisms of drug toxicity or intolerance

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Classically, adverse drug reactions had been considered as type A reactions which are related to the main pharmacological action of the drug and therefore are predictable (Rawlins and Thompson, 1985). Such reactions are predictable, reversible, and usually can be managed by lowering the dose of the offending drug. However, other adverse effects of drugs can occur which unrelated to the main pharmacological action of the drug. Such adverse effects are termed idiosyncratic and are often initiated by metabolites of the parent drug or by other indirect mechanisms. The detailed understanding of adverse drug events has become a major focus of the regulatory agencies throughout the world.

The pharmacotherapy of gastrointestinal and liver disorders is becoming increasingly complex. In recent years, with the advent of novel therapeutic agents to treat a host of disorders, including viral hepatitis, GI motility disorders, inflammatory bowel disease and others, the potential for serious clinically-relevant drug reactions has increased. In the pharmacotherapy of gastrointestinal and liver diseases, a significant number of adverse events that occur can be explained by drug interactions. Some pharmacokinetic drug interactions are based on the competitive inhibition of the rate of drug metabolism of one of the drugs, leading to an increased concentration of the drug which was not intended. In other examples, the interaction can be mechanistic in which one or more drugs when co-administered potentiate each others actions without any change in drug levels, termed pharmacodynamic interactions.

In this lecture, I will provide clinical examples of different types of drug interaction that are relevant to the clinician caring for patients with gastrointestinal and liver conditions. Those examples serve well to illustrate many of the relevant mechanisms and so will have clinical relevance beyond the specific drugs concerned.

Alcohol and smoking

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Consumption of alcoholic beverages and smoking are an element of daily life of people in many countries causing pleasures to the individual and great economic as well as tax revenues. However, the national economic and social costs for alcohol- and tobacco-related diseases far outweigh the advantages for the individual and the community. For example in Germany in 2008, the tax revenues were 3.3 billion Euro for alcohol and 13.5 billion Euro for tobacco, respectively, whereas the socio-economic costs for alcohol-related diseases added up to 24.4 billion Euro and for smoking-related diseases up to 33 billion Euro.

The WHO ranks smoking and alcohol consumption as first and third leading causes of the global burden of disease in industrialized countries, using Disability-Adjusted Life Years (DALYs) as a combined measure of premature death and disability. Smoking is responsible for 12.2% of all DALYs and alcohol consumption for 9.2%. For example in Germany, annually 110,000–140,000 humans die prematurely because of cigarette smoking and 40,000 because of alcohol drinking. In Europe and the USA, more than 20% of all hospitalized men and more than 9% of all hospitalized women suffer from alcohol-associated diseases. In Germany, about 2.0 million people in the age group of 18–64-year-old (3.8% of all Germans) are an alcohol abuser and 1.3 million people (2.4%) are alcohol-dependent. Alcohol can cause acute as well as chronic damage in nearly all body organs.

Smoking damages also nearly every human body organ and is worldwide the most important single preventable health risk factor as well as the main cause for premature mortality in industrial countries. One third of the adult Germans as well as of the world population are active smokers; men smoke more frequently than women (34.0% vs. 25.1%).

In this presentation a short overview will be presented on the most important deleterious effects of alcohol and smoking as well as on the underlying pathomechanisms. The most recent data about the pathophysiological relevance of non-alcoholic compounds of alcoholic beverages will also be discussed.

As far as the gastrointestinal tract is concerned alcohol mainly causes diseases of the liver (fatty liver, hepatitis, cirrhosis, carcinoma), the pancreas (pancreatitis), reflux esophagitis, various carcinoma of the upper aerodigestive tract, the liver and the colon.

There is a significant synergism between the effects of alcohol and smoking concerning malignant tumours of the mucosa in the oral cavity, pharynx, hypopharynx and esophagus as well as concerning pancreatitis, pancreatic cancer and hepatocellular carcinoma.

Moderate alcohol consumption (20 g ethanol/day for men and 10 g ethanol/day for women) is not as healthy as the published positive effects on ischemic

cardiovascular diseases and ischemic strokes might suggest. The same amounts of alcohol having positive effects on the heart and the brain increase the risk in women for getting breast cancer by 10% and for cancer of the upper aerodigestive tract by 30%.

The pathomechanisms of ethanol cannot be ascribed to a specific interaction with a distinct biochemical process. In the liver, ethanol is metabolized to acetaldehyde, which is responsible for most effects in human body after alcohol consumption. Acetaldehyde is also naturally present in tobacco. It is carcinogenic by forming adducts with DNA and by inhibiting the DNA repair processes. In addition, both smoking and drinking result in the formation of reactive oxygen species (ROS) which could result in DNA damage

The action of alcoholic beverages on the body is incompletely described if only the effect of ethanol is considered. In beer and wine for example, more than 2000 and 1000, respectively, non-alcoholic constituents are found. Non-alcoholic constituents, such as maleic acid and succinic acid, are responsible for the increase of gastric acid output in humans after consumption of fermented alcoholic beverages (e.g. beer, wine). In addition non-alcoholic constituents of beer are responsible for the stimulation of exocrine secretion of pancreatic acinar cells. In contrast, resveratrol and other polyphenols in alcoholic beverages have a protective effect on cardiovascular diseases.

Thus, more studies are needed to understand the interplay between ethanol and the other constituents in alcoholic beverages to understand their protective and damaging effects on human health.

Session IV

The liver as a target

Infections and the liver

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Hepatitis B and C virus has infected nearly half a billion individuals worldwide and are major indication for liver transplantation. Both viruses lead to liver cirrhosis, liver failure and the development of hepatocellular carcinoma with significant morbidity and mortality. For Hepatitis B virus infection which is characterized by a long period of latency, there are effective vaccination strategies and a potential hope of prevention of primary infection and reinfection of the liver allograft. However for the vast majority of patients, the aim is suppression of viral replication, viral load and liver injury. We have learned much from our initial experiences with nucleoside and nucleotide analogues in the treatment of this disease and the various factors that lead to viral resistance, the contribution from host susceptibility factors and the impact of co-infection with other viruses such as Delta agent and HIV.¹ This has led to a more rationalised strategy in the treatment of these patients with combinations of medications to prevent the emergence of resistant viral clones and greater efficacy with newer medications such as entecavir, telbivudine and tenofovir.¹ There has also been significant progress made with regards to preventing flares of acute hepatitis B virus in patients receiving biological therapies for rheumatoid arthritis and inflammatory bowel disease as well as the commencement of anti-cytotoxic therapies.¹

In hepatology, we have been slow to embrace the advances made in the treatment of HIV by utilizing combinations of therapy to target the virus and to lessen side effects. Hepatitis C virus is an excellent example of how our knowledge of this virus and the host factors involved in the clearance of this virus can be combined to greater clearance of the virus leading to a long term cure in most patients. The current standard of treatment for hepatitis C virus is pegylated Interferon therapy combined with Ribavirin to induce a potent host response to the virus. Unfortunately, hepatitis C virus consists of six main genotypes with more than 50 different subtypes. Individuals fortunate enough to suffer with genotype 2 or 3 can expect an 80% cure with current therapy whereas the more common genotype 1 is less amenable to combination therapy with less than 50% patients receiving a cure. One of the biggest disappointments in the treatment of hepatitis C has been the lack of an effective vaccine and is compounded by the huge ability of the virus to generate a multitude of quasispecies and mutants within the same individual. This is due to an error-prone proofreading function of its RNA polymerase. The net effect of this is that the immune system is unable to catch up with the most dominant subspecies and leads to eventual T cell exhaustion and the production of irrelevant antibodies presenting as cryoglobulinaemia. A key requirement to effective interference with hepatitis C virus biology is an adequate interferon response and has been highlighted by recent exciting events in three separate genome-wide associated studies. All three studies demonstrated that single nucleotide polymorphisms near or in the IL-28B gene location, all of which encodes for interferon-lambda3 had a large effect in determining the likelihood of patients obtaining a cure from Interferon and ribavirin combination therapy²⁻⁴ or spontaneous clearance of the virus⁵. Interferon-lambda3 is less potent than interferon-alpha in laboratory experiments but clearly, this polymorphism is an important determinant in response to therapy. 80% of patients who carry two copies

of this advantageous variant cleared the virus during interferon therapy and remained virus-free with a sustained viral response. This mutation is more common in Caucasian and Asian populations whereas it is only found in the 40% to 50% of sub-Saharan Africans who are known to be more resistant to combination therapy. The impact of this data is enormous as this paves the way for personalised medicine based on the genotype and a prediction of the likelihood of successful therapy. It is not inconceivable in the near future that not only the genotype but also the host factors will determine the appropriate regime and time scale of antiviral treatment.⁶

In contrast to understanding the host factors that determine progression and response to therapy, there have been significant strides made in targeting various stages of hepatitis C virus infection development and augmentation of the immune response. To this extent, the virus can be targeted at its entry level to the hepatocyte. This process involved interactions with CD81, claudin-1, scavenger receptor B1, the low density lipoprotein receptor and glycosaminoglycan. Similarly, the virus can be targeted once it's entered the cell by targeting its internal ribosomal entry site (IRES) or to target its helicase and protease enzymes with compounds such as telaprevir, boceprevir and trixalen. The NS5 section of the virus has also been targeted by directly targeting its polymerase with drugs such as filibuvir or direct inhibitors of the NS5A subunit. The polymerase enzyme of the virus can be targeted with a variety of mechanisms including nucleoside inhibitors such as valopicitabine or through non-nucleoside inhibitors all of which are currently being investigated in early phase studies. Appreciation of the host response and the value of enhancing the host response to the virus has not escaped the pharmaceutical development of novel drugs. The immune system can be boosted by selective immunisations with viral structures or by enhancing the adaptive immune response by activating dendritic cells with TLR 7,8 agonists as exploited by the compound resiquimod. This leads to activation of antigen-presenting cells, the programming of effector T cells and the production of cytokines such as interferon-alpha, IL-12 and TNF-alpha. Overall, successful cure in hepatitis C virus is possible and will require a personalized approach not only for the patient but also for the viral subtype.⁷

Although most of hepatology is dominated by hepatitis B and hepatitis C viral infection, these are by no means the only viruses that are able to exploit the immune system and cause liver damage. Both hepatitis A and E are major public health concerns in the developing world with many cases reported in the developed world as a consequence of faecal-oral infection. The majority of these cases are self-limiting. However, in selected populations, they lead to fulminant hepatitis requiring liver transplantation. The main reservoirs for replication of these enteric viruses are not only the liver but also cells of the intestine such as enterocytes.^{8,9} Recent work has shown that although these viruses are potentially damaging to the liver, much of their adverse effects in the liver is due to activation of the enteric immune system with an influx of activated gut-derived T cells in these livers with ensuing hepatitis. This allows the possibility of using medication that has been used to target inflammation in the gut predominantly for inflammatory bowel disease as a potential treatment for selected patients with severe liver injury.

Overall, the burden from viral-induced hepatitis is a large global public health problem. However, appreciation of the interaction between the host and the virus, and the appreciation of combination therapy to improve outcomes as well as lessen side effects is likely to significantly alter the way we target these infections in the future.

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Gallstones: Environment, life style and genes

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Gallstone disease represents one of the most common and costly gastroenterological disorders. In Germany, 0.25% of the population undergo cholecystectomy per year, and cholelithiasis incurs annual medical expenses of more than \$6.5 billion in the US. The paradigm of environmental risk factors for gallstones has lately been challenged by genetic studies in experimental models and humans. The analysis of more than 40.000 Swedish twin pairs with gallstones demonstrated that genetic factors account for 25% of the phenotypic variance. Since then, studies employing genome-wide association analysis, case-control cohorts and analysis of sib-pairs in families with gallstones have expanded our knowledge of "gallstone genes". Indeed, gallstone disease phenotypes are likely to result from the complex interaction of genetic factors, chronic overnutrition with carbohydrates, depletion of dietary fibre and other not fully defined environmental factors including physical inactivity and infections (Table 1). This hypothesis is supported by the profound increases of cholesterol gallstone prevalence rates in Native Americans, post-war European countries and current urban centres in East Asia, all of which were associated with "Westernized" nutrition. Herein, we summarize the spectrum of environmental and genetic risk factors, which should pave the way to "personalized" strategies for the prevention and therapy of gallstones.

Table 1: Environmental and life style risk factors for gallbladder stones

- High-caloric, low-fibre diet
- High-carbohydrate diet, dietary glycaemic load
- Physical inactivity
- Rapid weight loss / surgery for obesity
- Total gastrectomy with lymph node dissection
- Spinal cord injury
- Infections: enterohepatic *Helicobacter* spp., malaria
- Drugs: estrogens, octreotide, calcineurin inhibitors, fibrates
- Total parenteral nutrition
- Extended ileal resection (black pigment stones)
- Vitamin B₁₂-/folic acid-deficient diet (black pigment stones)

NASH and ASH

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Non-alcoholic Steatohepatitis (NASH) and Alcoholic Steatohepatitis (ASH) have similar pathogenesis and histopathology, but different etiology and epidemiology (1, 2). NASH and ASH are advanced stages of Non-alcoholic Fatty Liver Disease (NAFLD) and Alcoholic Fatty Liver Disease (AFLD) but the conditions causing the progression uncomplicated liver steatosis to NAFLD or ASH are presently unknown. NAFLD is a negative definition as it describes a disease characterized by excessive fat accumulation in the liver (steatosis), without any other evident causes of chronic liver diseases (viral, autoimmune, genetic, etc.), and with an alcohol consumption ≤ 20 g/day. On the contrary, AFLD is defined as the presence of steatosis induced by alcohol consumption greater > 20 g/day. Due to the negative definition of NAFLD/NASH there are some mixed situations due to both metabolic and alcoholic damage (NASH + ASH) that are still difficult to classify. Primary NAFLD/NASH is usually associated with insulin resistance (IR) and secondary NAFLD/NASH is due to a number of medical or surgical conditions or drug toxicity. The most common phenotypic manifestations of primary NAFLD/NASH are the same found in patients with the metabolic syndrome: overweight/obesity, visceral adiposity, type 2 diabetes, hypertriglyceridemia and hypertension. The prevalence of NAFLD in the general population in Western countries is estimated to be 25–30%, increases with age, is highest in males between 40 and 65 years, and is higher in Hispanics and lower in African-Americans. The prevalence and the incidence of NASH and ASH are not known because of the impossibility of performing liver biopsy in the general population. Up to 90% of alcoholics have FL, and 5–15% of these subjects will develop cirrhosis over 20 years. The risk of cirrhosis increases to 30–40% in those who continue to drink alcohol. About 10–35% of alcoholics exhibit changes on liver biopsy consistent with alcoholic hepatitis. If the alcohol intake is stopped, 10% of the patients fully reverse both the histological changes and liver enzymes. The natural history of NASH is not completely defined, even if patients with NASH have a reduced life expectancy due to liver-related death and cardiovascular diseases. The best treatment of AFLD/ASH is to stop drinking alcohol and the most effective first-line therapeutic option for NAFLD/NASH is non-pharmacologic lifestyle interventions through a multidisciplinary approach including weight loss, dietary changes, physical exercise, and cognitive-behaviour therapy. A recent large multicenter randomized clinical trials showed that vitamin E may be effective in treatment of some NASH histological features but not the most important one, i.e. fibrosis.

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State-of-the-Art Lecture

What need gastroenterologists to learn from epidemiology?

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Despite the fact that the birth of modern epidemiology, Dr. John Snow's 1851 discovery of the Broad Street water pump in central London as the source of a cholera outbreak, had a gastrointestinal focus, epidemiology did not play a major role in the specialty of gastroenterology for many years. If a single event brought home to gastroenterologists the importance of epidemiology in the understanding of gastrointestinal disease, it was the discovery of *Helicobacter pylori* infection as the cause of peptic ulcer disease and gastric cancer in the 1980s. It is difficult to explain to physicians who trained after the mid-1990s how this event resulted in a major paradigm shift of both research focus and treatment. The past twenty-five years have seen remarkable advances in understanding of pathogenesis and treatment of numerous diseases within the specialties of gastroenterology and hepatology, and one could argue that many of these advances were made possible in part through the use of epidemiological tools. Examples to name just a few include: the identification of post-transfusion non-A non B hepatitis (subsequently identified as hepatitis C); the discovery of Nod 2/CARD15 and other susceptibility genes in inflammatory bowel disease, and the discovery of "permissive" HLA haplotypes for celiac disease. Refinement in epidemiological techniques (e.g., systematic reviews, meta-analyses, instruments measuring health-related quality of life/patient-reported outcomes, decision analysis models, availability of large databases, advances in nutritional and genetic epidemiology) have aided this progress.

There has been increasing recognition of the deleterious effects of excess caloric intake and obesity on the gastrointestinal tract. Obesity not only increases the risk of non-alcoholic fatty liver disease and cryptogenic cirrhosis, it is associated with increased risk of multiple gastrointestinal cancers (e.g., esophageal, colorectal, hepatocellular, pancreatic). Furthermore, specific dietary factors may influence the risk of gastrointestinal disease (e.g., red meat and colorectal cancer, alcohol as a cofactor for chronic viral hepatitis-related liver disease, protective effect of coffee and tea for cirrhosis, proton-pump inhibitors and drug-induced microscopic colitis).

The field of epidemiology has yielded a few clues to the pathogenesis of several as-yet idiopathic gastrointestinal conditions. For example, several lines of evidence suggest that alterations in one's environment early in life might influence the risk of ulcerative colitis or Crohn's disease, and that this may be mediated through alterations in the fecal microbiome. Epidemiologic tools also enable us to better characterize the natural history of chronic gastrointestinal conditions such as inflammatory bowel disease, and it is hoped that this will ultimately result in the development of risk stratification tools that will allow physicians to better target high-risk patients with more effective therapies.

It is hoped that continued efforts in the area of gastrointestinal epidemiology will help unlock pathogenic mechanisms and improve treatments in this area. For some of the more widespread and costly conditions, even mild reductions in the incidence and severity of gastrointestinal illness will result in thousands of patients with better quality of life and millions of euros/dollars spent on other efforts.

Suggested reading:

GI Epidemiology. Talley NJ, Locke GR, Saito YA, editors. Wiley-Blackwell, 2007, 1st edition. ISBN: 978-1-4051-4949-5.

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Herbert Falk award lecture

From aphthous ulcer to full blown Crohn's disease

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Early Crohn's disease is characterized by a purely inflammatory phenotype but in the course of the evolution of the disease stricturing and perforating complications occur. To investigate the pathogenesis of the disease we need to focus on the earliest lesions. The aphthous ulcer has been identified as an early lesion (1) and this type of lesion occurs also at a distance of more severely involved and ulcerated segments in later Crohn's disease. We have shown that the early stage of Crohn's disease can best be studied in the postoperative Crohn's disease recurrence model. Recurrent lesions can be visualised as early as a few weeks to months after curative ileocolonic resection in the neoterminal ileum just proximal to the anastomosis (2) with a post-anastomotic colon mostly free of macroscopic disease. It is not at all clear what makes the ileal mucosa just proximal to the anastomosis so vulnerable to recurrent lesions. The combined presence of bacteria and bile acids, the break in the mucosa of the suture, reflux of colonic contents and the organisation of the mucosal immune cells may be contributing factors.

We have shown that the severity of early recurrent lesions predicts the subsequent clinical evolution in patients with Crohn's disease who underwent curative resection of the involved ileocolonic segment (3). This endoscopic and clinical progression of early recurrent lesions to full blown disease can be slowed by the administration of nitro-imidazol antibiotics (4–5).

The trigger for development of recurrent lesions is probably a luminal factor (6). We were able to show in five patients that as long as the ileocolonic anastomosis was protected by a proximal ileostoma and no fecal stream passed through the anastomosis Crohn's lesions did not recur. As soon, however, as the bowel continuity was restored recurrent ulcers developed in the neoterminal ileum and the evolution of the disease resumed its natural course. Our group also showed that infusion of ileal contents in the excluded bowel (7) triggered new inflammatory lesions within days. We have now extended these studies to a group of 19 patients who underwent temporary diversion proximally to the ileocolic anastomosis. None of the patients developed recurrent Crohn's disease in the neoterminal ileum during diversion whereas 13/14 of the patients who underwent re-anastomosis developed recurrent lesions in the neoterminal ileum within 3-6 months after re-anastomosis.

We think that the evolution of the postoperative recurrence of Crohn's disease mimics the natural evolution of Crohn's disease at its onset. This goes from pre-ulcerative inflammation over aphthous ulcers to more extensive ulceration and nodularity to result in complications including stenosis and fissures which can be complicated by abscesses and fistulae. Even the symptom free interval after surgery might mirror the pre-symptomatic phase at the onset of the disease in the same way as the extent of recurrent Crohn's disease seems to correlate with the length of primary involvement of the small bowel.

Our group showed that whereas inflammatory lesions at the section margins overall are not predictive of recurrence peri-neural inflammatory changes in contrast predict

recurrence (8). Peri-neural inflammation might represent a way the inflammation spreads after resection.

Recently we have used mucosal gene profiles to identify mucosal gene signatures predictive for response to biological therapy in UC and CD (9–10) and we are now applying these techniques to perform gene profiling of the mucosal biopsies during exclusion in comparison with gene array studies of early recurrence in the mucosa after restoration of the bowel continuity. In recent years new tools have also become available for the study of the composition of the luminal and mucosal flora of the gut. We are currently using these tools (11) for investigating the differences in the luminal and mucosal flora of the ileum after ileocolonic resection with diverting stoma in comparison with patients with ileostomy for other indications.

Further studies of the microenvironment of the mucosa in the postoperative recurrence model should lead to more insight in the pathogenesis of Crohn's disease.

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Session V

The gut as target

Irritable bowel syndrome: Gender, infection, life style or what else?

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Irritable bowel syndrome is characterised by abdominal pain and an erratic bowel habit, which depending on the definition affects 5–10% of the population. As a typical complex disease it is expected that any genetic contribution will be made up of many small effects with important environmental interactions. Twin studies support this idea with maternal behaviour an important environmental influence. Other environmental factors include infection, diet and psychological stressors. Most studies agree the incidence peaks in the 20's and 30's and is commoner in women than men¹. Prospective studies indicate that illness, behaviour, anxiety and somatic symptoms are independent predictors of new onset IBS². Other prospective studies show female gender and lower quality of life as an important risk factor³ while ongoing chronic stress predicts a poor prognosis⁴. However a large population based study showed that gastroenteritis was one of the strongest risk factors for developing IBS⁵. Several subsequent prospective studies have confirmed the increased risk of IBS following infection which depends on the severity and type of gastroenteritis⁶. Bacterial toxicity increases the risk substantially⁷ while a meta-analysis confirms that the average incidence of post infective IBS is 10% with younger age, anxiety and depression independent risk factors⁸. Several studies have confirmed an increased permeability following infection though whether this is a marker of inflammation or important in the causation of symptoms is unclear. Recent genetic studies point to the importance of the response to bacteria via the Toll-like receptor 9, cytokine responses (IL-6) and genetic predisposition to develop increased permeability as independent risk factors though the severity of the illness exerts a much larger effect⁹. Recent studies suggest that psychological factors by activating the innate immune system can increase gut permeability but whether this is important in symptoms remains controversial. These data confirm that IBS is a multifactorial condition with important contributions from both genetic and environmental factors.

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Inflammatory bowel disease: Which lifestyle factors are of importance?

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The incidence of Inflammatory Bowel Diseases has increased markedly during the last 60 years in the western world, and more recently in the developing countries. Changes in environmental factors, and among them, particularly lifestyle factors, may explain this increased incidence. Moreover, it has been shown that these factors may also modify disease course. The best characterized lifestyle factor in IBD is smoking. Current smoking increases the risk of developing Crohn's disease and worsens its course, increasing the need for steroids, immunosuppressants, and re-operations. Smoking cessation has a beneficial effect on disease course, decreasing the risk of flares. Achieving smoking cessation in Crohn's disease is thus an important goal of therapy. On the contrary, smoking protects against Ulcerative Colitis and after disease onset improves its course, decreasing the need for colectomy. Smoking cessation increases the risk of flare and the need for steroids or immunosuppressants. However patients with Ulcerative Colitis should not be discouraged to quit, because the beneficial effect of smoking for their disease is counterbalanced by the deleterious respiratory and cardiovascular effects of tobacco. Other lifestyle factors of importance are the diet and physical activity, although there is no evidence that exercise has any effect on disease activity. Physical activity may improve quality of life and may contribute to increase muscle mass and to prevent osteoporosis. Regarding nutrition, a western diet may be associated with an increased risk of IBD, and a case-control prospective study nested in the EPIC-study revealed an increased consumption of linoleic acid (present in red meat and corn and sunflower oils) before diagnosis of Ulcerative Colitis. Finally, obesity is becoming more prevalent in IBD, complicate therapy as steroids should be avoided, and in Crohn's disease may be associated with higher disease activity and perianal complications.

Colon cancer – A civilization disorder

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Colorectal cancer arises in individuals with acquired or inherited genetic predisposition who are exposed to a range of risk factors. Many of these risk factors are associated with affluent western societies. More than 95% of colorectal cancers are sporadic arising in individuals without a significant hereditary risk.

Geographic variation in the incidence of colorectal cancer is considerable with a higher incidence observed in the West. Environmental factors contribute substantially to this variation. A number of these risk factors are associated with a Western lifestyle and could be considered a product of “civilization”. Recently, smoking has been recognized as a risk factor. Energy consumption also influences colorectal cancer risk with obesity increasing risk and exercise reducing risk. However, the strongest contribution to environmental risk for colorectal cancer is dietary. Consumption of fat, alcohol and red meat is associated with an increased risk. Fresh fruit and vegetables and dietary fibre are protective. There are also risk factors not associated with lifestyle but rather with disease and include Inflammatory Bowel Disease and Primary Sclerosing Cholangitis.

Much has been learnt recently about the molecular pathogenesis of colorectal cancer. Colorectal cancer always arises in the context of genomic instability. There is inactivation of the tumour suppressor genes APC, p53, TGF- β , activation of Ras and PI3 Kinase oncogene pathways and the COX, Epidermal growth factor, VEGF Growth factor pathways. The mechanisms by which environmental factors modify the mutation risk in these pathways are poorly understood, but micronutrient deficiency, mitochondrial modulation and altered gut bacterial-epithelial interaction may all have a role.

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Session VI

Upper GI-tract and pancreas as a target

Epidemiology of gastroesophageal reflux disease

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Overview: Gastroesophageal reflux disease (GERD) is comprised of a spectrum of related disorders, including hiatal hernia, reflux disease with its associated symptoms, erosive esophagitis, peptic stricture, Barrett's esophagus, and esophageal adenocarcinoma. Besides multiple patho-physiological associations among these disorders, they are also characterized by their comorbid occurrence in identical patients and by their similar epidemiologic behavior. The occurrence of GERD is shaped by marked temporal and geographic variations, suggesting the influence of environmental risk factors in the etiology of these diseases.

Variations by time, geography, and race: Between 1975 and 2005, the incidence of esophageal adenocarcinoma has increased five-fold in the U.S. This increase has been more pronounced in whites than nonwhites. Although esophageal adenocarcinoma is generally about four times more common in men than women, the increase in the incidence has affected men and women alike. Such increase in incidence is not restricted to data from the U.S., but has been observed similarly in most European countries as well. In general, all forms of GERD occur less frequently in non-Western countries. The prevalence of GERD appears to be rising in the most developed countries of Asia, such as Japan, Singapore, and Hong Kong, with a concomitant rise in adenocarcinoma. In the U.S., multiple studies have shown consistently esophageal adenocarcinoma to be twice more common among whites than other ethnic groups, such as blacks and Hispanics. Similar variations apply to other forms of GERD, such as Barrett's esophagus and erosive esophagitis.

Affluence and obesity as risk factors: In the U.S., all forms of GERD and, especially, Barrett's esophagus and esophageal adenocarcinoma tend to occur slightly more often in subjects with higher income. Affluence as a risk factor appears to exert its influence independently of ethnicity. Overweight and obesity contribute to the development of hiatal hernia, increase intra-abdominal pressure, and promote gastroesophageal reflux. Multiple investigators have shown that being overweight or obese is a risk factor for the occurrence of reflux symptoms, erosive esophagitis, Barrett's esophagus, and esophageal adenocarcinoma. Weight gain has been shown to increase reflux symptoms, whereas weight loss decreases such symptoms. Within the U.S., there are strong correlations between the prevalence of obesity and GERD-related hospitalizations. Hospitalizations associated with a primary or secondary discharge diagnosis of reflux disease occur more frequently in states where obesity prevalence is high. Most likely, other risk factors, such as smoking, alcohol, dietary fat, or drugs, play only a minor role in shaping the epidemiologic patterns of GERD.

Protection through *Helicobacter pylori*: On a population level, a high prevalence of *H. pylori* infection is likely to reduce levels of acid secretion and protect some carriers of the infection against reflux disease and its associated complications, such as peptic stricture, Barrett's esophagus, and esophageal adenocarcinoma. Several studies have confirmed lesser prevalence rates of *H. pylori* among subjects with than without GERD. It also appears that CagA-positive *H. pylori* strains are more

protective against reflux disease than CagA-negative strains. The prevalence of *H. pylori* infection correlates with standards of hygiene and economic development. Until recently, populations in Africa and Asia may have been protected against the development of GERD and esophageal adenocarcinoma by their higher prevalence rates of *H. pylori* infection.

Conclusions: The study of environmental risk factors may provide an opportunity to better understand GERD, as well as esophageal adenocarcinoma, and develop a means of their prevention.

Chronic pancreatitis and pancreatic cancer – Environmental and genetic factors

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Chronic pancreatitis

Chronic pancreatitis is defined as a continuous or recurrent inflammatory disease of the pancreas characterized by progressive and irreversible morphological changes. It typically causes pain and permanent impairment of pancreatic function. In chronic pancreatitis areas of focal necrosis are typically followed by perilobular and intralobular fibrosis of the parenchyma, by stone formation in the pancreatic duct and by the development of pseudocysts. Late in the course of the disease a progressive loss of endocrine and exocrine function occurs. Several attempts have been undertaken to establish histological and morphological criteria to clearly define chronic pancreatitis. Unfortunately an exact correlation between clinical symptoms, morphological signs and histological criteria does not exist. With an incidence of 8.2, a prevalence of 27.4 per 100,000 and a frequency of 0.04% to 5% in autopsies chronic pancreatitis represents a common disorder of the gastrointestinal tract. Chronic pancreatitis accounts for a substantial morbidity and health care costs. The annual treatment costs per patient are approximately 17,000 \$. 20,000 Americans are admitted to hospital every year with chronic pancreatitis and about three times as many are discharged with the diagnosis chronic pancreatitis. The 10 year survival rate of patients suffering from alcohol-induced chronic pancreatitis is 70%, while the 20 year survival rate is 45%. The mortality is thus 3.6 fold increased compared to a cohort without chronic pancreatitis.

Environmental factors of chronic pancreatitis

In Western countries alcohol consumption is assumed to be the leading cause (70–90%) of chronic pancreatitis. According to studies from Marseille, the relative risk of chronic pancreatitis increases as a function of the quantity of alcohol and protein consumed. There seems to be no threshold toxicity of alcohol as reported in alcoholic liver damage. The type of alcoholic beverages consumed appears to be less relevant than in liver disease. Patients with chronic pancreatitis and alcohol-induced liver cirrhosis do not differ with regard to their daily intake of alcohol. However the duration of alcohol consumption is shorter in chronic pancreatitis. In most studies the time between the onset of alcohol abuse and first symptoms is 18 years. The prevalence of chronic pancreatitis clearly correlates with alcohol consumption in a given population. An increasingly recognized factor in the etiology of pancreatitis is smoking and tobacco use. While alcohol use is presently overestimated as a potential cause for pancreatitis, smoking is underestimated and recent population-based studies suggest that the role of smoking in pancreatitis may be even greater than that of alcohol. Other external factors that have been proposed to contribute to the risk of developing pancreatitis are nutritional components such as foods high in animal fat, foods low in minerals and trace elements and foods low in oxygen radical scavengers.

Genetic factors for chronic pancreatitis

Much better understood are the genetic changes that predispose to pancreatitis and include clearcut autosomal dominant inheritance patterns as well as low abundance

risk factors. Genetic changes that have been associated with an increased risk of pancreatitis or with a decreased risk of pancreatitis are cationic trypsinogen (PRSS1), the cystic fibrosis transmembrane conductance regulators (CFTR), anionic trypsinogen (PRSS2), pancreatic secretory inhibitor (SPINK1), Chymotrypsinogen C (CTRC), Calcium Sensing Receptor (CASR), Cathepsin B (CTSB) and Ubiquitin Ligase E3 α (UBR1).

Pancreatic cancer

Pancreatic cancer is a devastating disorder from which most affected patients die. It has the worst survival rate of any major cancer. In the US 30,700 patients will be diagnosed with, and 30,000 Americans will die from, pancreatic cancer in 2010. World-wide estimates for the year 2010 by the World Health Organization show an incidence of 201,506 cases and 200,865 deaths and demonstrate the near-universal lethality of this disease. Survival rates are somewhat stage dependent with a 5-year survival rate of only 20% for local disease. However, only a minority of patients presents with local disease. This is a result of our inability to diagnose pancreatic cancer early by symptoms alone and our current lack of a blood test or imaging test that can accurately detect a cancer prior to symptom onset in the general population. Although the low incidence of pancreatic cancer in the general population does not make it practical to screen for pancreatic cancer at present, high-risk groups can be identified which may benefit from surveillance by detecting a tumour at an earlier, hopefully more curable stage. The most promising of those are subjects/patients from families in which a definitive gene has been identified, that conveys an increased risk of developing pancreatic cancer and can be tested for. In addition to hereditary pancreatitis, which increases the pancreatic cancer risk 40–70 fold, the following cancer syndromes fall into that category.

Genetic factors

A number of germline mutations and hereditary syndromes have been associated with an increased risk of developing pancreatic cancer. These include patients with Hereditary Breast and Ovarian Cancer Syndrome (HBOC) who have a hereditary predisposition to early onset breast and ovarian cancer. Other cancers associated with this syndrome are prostate, colon, and pancreatic cancer. Women diagnosed with HBOC have an approximate 80% lifetime risk of developing breast cancer and an approximate 40% lifetime risk of developing ovarian cancer whereas the risk of developing pancreatic cancer increases around 10 fold. Mutations involve the BRCA1 gene on 17q21 and the BRCA2 gene on 13q12-q13. A very high risk is associated with Peutz-Jeghers syndrome (PJS). Individuals affected with Peutz-Jeghers syndrome have multiple gastrointestinal hamartomatous polyps and mucocutaneous pigmentation. Individuals with PJS are at increased risk for developing cancer of the pancreas, colon, breast, endometrial, ovarian, lung, or testes. The relative risk for developing pancreatic cancer is increased 100 fold. The STK11/LKB1 gene on chromosome 19p13.3 is affected.

HNPCC is a condition that is characterized by an increased risk of colon cancer and other cancers that include cancers of endometrium, ovary, stomach, small intestines, hepatobiliary tract, upper urinary tract, brain, and skin. Individuals diagnosed with HNPCC have an approximate 80% chance of developing colon cancer in their lifetime. The average age of onset for colorectal cancer in these individuals is 44 years. Women diagnosed with HNPCC have a 20–60% chance of developing

endometrial cancer in their lifetime with an average of diagnosis of 46 years. HNPCC increases the risk for pancreatic cancer only up to twofold and the affected genes are MLH1 and MSH2. Another hereditary disorder is Familial Atypical Multiple Mole Melanoma (FAMMM). Individuals with FAMMM have a familial predisposition to developing atypical moles that can develop into melanoma. Melanoma can also develop de novo in these individuals. The average age of initial melanoma diagnosis is 34 years. Those diagnosed with FAMMM may have an increased risk of developing pancreatic cancer and astrocytomas. The risk for pancreatic cancer increases 13–22 fold and the affected gene is P16INK4 on chromosome 9p21. One of the highest risk for developing pancreatic cancer is conveyed by hereditary pancreatitis (40–70%). Mutations in the cationic trypsinogen gene (PRSS1) are regarded as causative for developing hereditary pancreatitis and when HP-patients smoke they double their risk of developing pancreatic cancer.

Environmental factors

Epidemiological studies on environmental factors that increase the risk of pancreatic cancer are often contradictory. While obesity or an increased body mass index have been shown conclusively to increase the risk of pancreatic cancer in Western countries, they do not seem to do so in Japan where obesity is much less prevalent. Recent onset diabetes mellitus in patients over 50 years of age is also associated with an increased risk for developing pancreatic cancer over the subsequent years, although this increased risk is so low (about twofold) and the prevalence of adult onset diabetes so high, that screening efforts cannot be based on this observation. Alcohol, in itself, does not seem to be an independent and direct risk factor for pancreatic cancer, although chronic pancreatitis is. However, in population based studies, rather than disease based cohort studies, the risk for developing pancreatic cancer as a consequence of chronic pancreatitis is so low (0.5% over 20 years) that the sequence: immoderate alcohol consumption (5–10%) leading to chronic pancreatitis (5%), leading to pancreatic cancer (0.5%) cannot statistically be demonstrated in population-based studies of less than a million participants. That is not true for tobacco use and smoking which are responsible for a significant number of cases with pancreatic cancer and represents the statistically most important (and preventable) environmental factor for the disease. Possibly *Helicobacter pylori* infection represent an additional risk factor. What patients cannot change is their heritage. Being male or decendent from Africans or Ashkenasi Jews increases your risk of developing pancreatic cancer.

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Session VII

Implications for treatment

Hepatobiliary disorders

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The last two decades have witnessed a considerable progress in the understanding of the mechanisms responsible for the fibrogenic progression of chronic liver diseases, including those characterized by chronic biliary damage. Besides the remarkable advances in the development of antiviral drugs for the treatment of liver diseases sustained by chronic HBV and HCV infections, two major areas are currently regarded as potentially important from the therapeutic point of view: the development and the evaluation of anti-fibrotic agents and the advances in the biology of nuclear receptors.

The search for effective antifibrogenic strategies is based on the knowledge gained in the area of hepatic stellate cell (HSC) biology, including the biology of the factors (growth factors, cytokines, etc.) conditioning their profibrogenic attitude. Indeed, the well-described pathway of HSC activation, subsequent fibrogenesis, with the potential for apoptosis and reversibility, provides a logical framework to define sites of intervention. Putative antifibrogenic drugs include: 1. agents able to reduce inflammation and immune response, 2. agents able to reduce the activation of ECM-producing cells and their profibrogenic properties (proliferation, motility, ECM deposition, contraction), 3. agents with pro-apoptotic potential for ECM-producing cells, 4. agents able to increase fibrillar ECM degradation. It should be stressed that most of the evidence indicating a beneficial effect of these drugs derives from studies performed in vitro or in animal models of fibrogenesis. Therefore it is still debatable whether or not these agents could be truly effective. Considering the above limitations, it is about time to select some of the most promising agents emerging from preclinical studies and start testing their clinical efficacy. However, testing for clinical efficacy may prove difficult and expensive. Appropriate end-points for studies need to be defined and agreed as the time frame for regression of fibrosis is likely to be adequately measurable only in years. Consequently, the relative need to set long-term prospective studies represents a major limitation for the enthusiasm of researchers embarking in this task. Since all CLDs are in general characterized by a very slow course to cirrhosis, the above mentioned limitations contrast with the possibility that any suitable antifibrogenic treatment could effectively render the fibrogenic evolution even slower and eventually reduce the number of patients reaching end-stage disease within a reasonable life time-frame.

The biology of nuclear receptors HSC, represents a relevant area of investigation, with potentially important acquisitions for the therapy of chronic liver disease. A key issue is represented by the variable expression of different nuclear receptors in quiescent (i.e. representing the condition in normal liver tissue) and activated, myofibroblast-like HSC (i.e. representing the condition in liver tissue with active fibrogenesis). The prototype of this variability is PPARgamma, whose expression progressively decreases during the process of HSC activation. PPARgamma down-regulation is associated with an increased profibrogenic action of activated HSC in reason of increased activity of transcription factors, e.g. AP-1, modulating key pro-fibrogenic genes such as procollagen I and TIMP-1. More in general, PPARgamma down-regulation is related with a transition of HSC from an “adipogenic” to a “fibrogenic” phenotype. In line with this, a de-novo induced expression of

PPARgamma in activated HSC reduces the expression of activation markers and restores the ability to accumulate retinyl esters. Based on these on other *in vitro* evidences, several studies performed in animal models have shown that administration of synthetic PPARgamma-ligands such as thiazolidinediones effectively suppress the fibrogenic activity of activated HSC, but only when the drug is administered concomitantly with the causative agent of liver tissue damage. On the contrary, the effects of synthetic PPARgamma ligands on established fibrosis are very scarce or absent, confirming a low residual expression of this nuclear receptor in activated fibrogenic cells and raising scepticism on the use of this class of drugs as antifibrotics in clinical practice.

Expression, function and possible pharmacological manipulation of another nuclear receptor, i.e. FXR, has received high priority in the last few years. FXR biology has been shown to be very relevant for bile secretion, lipid and carbohydrate metabolism. In addition, studies performed in rat HSC have shown that stimulation with synthetic FXR agonists results in important antifibrogenic actions, including a restoration of PPARgamma expression and function. Differently from PPARgamma, FXR expression becomes up-regulated during rat HSC activation, thus making any pharmacological strategy able to stimulate FXR a theoretical golden bullet to counteract hepatic fibrogenesis. This possibility still awaits confirmation in humans. Regardless, *in vitro* data obtained in several preparations of human activated HSC indicate that the expression of FXR is absent or very low. This raises a general concern when transferring *in vitro* and *in vivo* evidence obtained in rodents to human chronic liver diseases.

A possible role for other nuclear receptors, and in particular PXR, LXR and CAR has been suggested by recent studies and needs to be further exploited.

Environmental and lifestyle influences on disorders of the large and small intestine – Implications for treatment

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There is growing evidence that many aspects of our lifestyle and the environment we now live in contribute to the development of disease. The luminal digestive tract is a clear target of the influence of dietary components, alcohol, microbial organisms, and other ingested materials. External factors including obesity, lack of physical exercise, and tobacco consumption also impact diseases of the luminal GI tract. A growing understanding of the microbiome which forms an integral part of the human organism indicates that this is another important external force that impacts human health and disease. The luminal GI tract conditions that arise, at least in part, from these external factors range from malignancies (squamous cell esophageal cancer, Barrett esophagus and associated esophageal adenocarcinoma, gastric cancer, and colorectal cancer [CRC]), idiopathic inflammatory disorders such as inflammatory bowel diseases (IBD), and post-infectious syndromes including post-infectious IBS, post-infectious dyspepsia and other functional GI disorders. Of particular interest given their increasing in prevalence in much of the world, are immune-mediated conditions in which food antigens are the driving force behind their development. These entities include celiac disease, eosinophilic esophagitis, and food allergies.

Celiac disease is a prime example of a condition mediated by dietary factors whose pathogenesis has only recently been determined providing opportunities for treatment options beyond the gluten-free diet. While a genetic basis for disease clearly exists, it is believed that environmental factors such as an increase in gluten in the human diet account for its rising prevalence, now over one percent of genetically susceptible populations in all continents. Proposed therapeutic strategies span from preventing disease by modulating the time of gluten introduction in infants, to reducing exposure to gluten by developing strains of wheat with lower levels of gluten, degrading ingested gluten peptides within the intestinal lumen via endopeptidases or modulating uptake of these peptides across intestinal tight junctions. Other novel treatments in development focus on interfering with the immune events that lead to disease once gluten accesses the lamina propria including altering the immune milieu from a Th1 predominant response via hookworm infection, inhibiting tissue transglutaminase, and blocking antigen presentation and/or T cell responses to gluten peptides.

While new treatment options for celiac disease reflect the complex interaction of diet, genetic factors and the host immune response, the implications for treatment of many conditions of the large and small intestine that arise from environmental and lifestyle are as basic as ensuring adequate nutrition, regular exercise and cessation of tobacco use. Much more needs to be learned about the microbiome, dietary and other factors and their interaction with the human host in order to develop potential new treatment strategies for diseases that result from the environment and lifestyle.

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Disorders of the upper GI-tract and the pancreas

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Epidemiology

Esophagus

There are two main histological types of esophageal cancer, squamous cell carcinoma and adenocarcinoma. Tobacco smoking, excessive alcohol consumption, low intake of fresh fruits and vegetables and achalasia increase the risk for esophageal squamous cell carcinoma. The incidence of esophageal adenocarcinoma is increasing in the western world while the incidence of esophageal squamous carcinoma remains unchanged or is decreasing. The Barrett esophagus which is the precursor is characterized by the replacement of squamous epithelium of the distal esophagus by columnar epithelium and mucus-secreting goblet cells. 10–20% of patients with reflux disease develop this specialized intestinal metaplasia in the distal esophagus. Barrett's esophagus with dysplasia has a 30 to 125 times increased risk of adenocarcinoma compared to the general population. Long-segment Barrett is over 3 cm and has a higher risk than short-segment Barrett.

There is an association of several environmental factors with the increase of esophageal adenocarcinoma including diet, obesity, and chemical exposure. A number of studies have demonstrated that gastroesophageal acid reflux (GERD) is the main risk factor. Other environmental factors are non-steroidal anti-inflammatory drugs (NSAIDs), nitrosamines and *H. pylori*. In addition family predisposition have been shown to be implicated. Esophageal adenocarcinoma increases with higher BMI, growing obesity and explains the rising increase. Although major environmental risk factors have been identified cellular mechanisms contributing to cancer development are poorly understood.

Stomach

Gastric cancer is a worldwide health burden. Gastric cancer is caused by the interaction of environmental exposures, *H. pylori* and host factors. *H. pylori* infection is generally acquired during childhood and can persist for the lifetime of the host. In gastric cancer *H. pylori* induces inflammation in the corpus, multifocal gastric atrophy and low levels of acid secretion. IL-1 β is induced by *H. pylori* and contributes to the inhibition of acid secretion. There is a possible interaction between *H. pylori* infection and smoking as well as dietary antioxidants. An adequate intake of fruits and vegetables appears to lower the risk with ascorbic acid, carotenoids, folates and tocopherols acting as antioxidants. In the Asian population *H. pylori* and high dietary salt intake may have a higher risk than subjects with low salt intake. The incidence of gastric adenocarcinoma is declining worldwide.

Pancreas

More than 250,000 patients die each year of pancreatic cancer. Epidemiologic studies found a positive association with family history and cigarette smoking. There is an association with diabetes mellitus and chronic pancreatitis. The data are inconsistent for red meat, sugar, fat, body mass index, gallstones, and *H. pylori*. The protective effect of parity, dietary folate, aspirin, and statins has not been

demonstrated. There is no evidence for linking alcohol or coffee consumption with an increased risk of pancreatic cancer.

Inflammation-cancer association

The observation that inflammation might be a cause of cancer development was already reported by Virchow in 1850s. Chronic inflammation promotes cancer by a variety of mechanisms and inflammation orchestrates the tumor microenvironment. Chronic inflammation is caused by various environmental factors including chemical injury and exposure to irritants. Injuries trigger a cellular response with cellular infiltrations (neutrophils, macrophages, natural killer cells etc.), cytokines and the production of reactive oxygen species (ROS).

This has been shown for the development of esophageal cancer in patients with gastrointestinal reflux and Barrett's esophagus, gastric cancer in patients with chronic gastritis, hepatocellular carcinoma in patients with chronic hepatitis, cholangiocarcinoma in patients with sclerosing cholangitis, colon cancer in patients with ulcerative colitis and pancreatitis cancer in patients with chronic pancreatitis. This process usually takes decades since multiple hits seem to be necessary to inactivate tumor suppressor genes and activate oncogenes to finally drive cancer development.

Esophagus

Initially gastric reflux was suggested to be the responsible agent for the development of Barrett mucosa and adenocarcinoma. Novel data favor bile acid exposure to be of critical importance for mucosal damage, esophagitis and Barrett's disease. Bile acid content in the refluxate is increased in individuals on high fat diet. Bile acid reflux has been demonstrated in patients in the absence of acid reflux. Up to now it is not clear whether bile acids or acid may individually cause esophageal injury or both agents may have a synergistic effect. Esophageal injury induces a chronic inflammation of the squamous epithelium which can either be replaced by squamous cells or be replaced by Barrett mucosa. Chronic inflammation causes a local increase of cytokines, chemokines, prostaglandins and ROS known to promote cell growth, cell migration, mutagenesis, increased angiogenesis and finally initiation of tumor development and progression.

Stomach

It has recently reported that *H. pylori* infection of gastric epithelium induced the expression of the activation-induced cytidine deaminase gene, a gene linked to hypermutation which may predispose to point mutations in tumor suppressor genes. Although there are numerous studies, the exact mechanism underlying malignant transformation by *H. pylori* is unclear. The effect of *H. pylori* on the gastric barrier function, increase genetic instability through ROS, limited mucosal defense and reduced apoptosis might all more or less contribute to changes leading to tumor initiation and progression.

Pancreas

The association between chronic pancreatitis and pancreatic cancer is not very strong since patients with long standing chronic pancreatitis have a high morbidity and mortality. In fact in almost all studies more than 90% of patients with chronic pancreatitis die not from pancreatic cancer. Moreover most cases of pancreatic cancer develop in patients without clinical evidence of chronic pancreatitis.

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State-of-the-Art Lecture

Diseases of the digestive tract – Is prevention possible and feasible?

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In my opinion, the answer is clear. Prevention is, and should remain as one of our major professional goals. Ideally, disease should never catch us by surprise. If it does, the outcome is uncertain, costs blow up and success is compromised. Another issue, of course, is whether at present we have the technical and financial means to undertake efficient program prevention for GI disease. That is, approaches we can honestly recommend to the populations at risk to true advantage. I would contend that for certain conditions/groups we indeed have such means in 2010. However, even more important, we have a substantial knowledge base to feasibly make decisive progress in the next 5–15 years.

So, how do we go about this enormous but critically important prevention task? Logically we must take first a broad by systematic look at the conditions we aim to prevent and prioritize based on need and probability to succeed. Second, we must examine and promote life style measures that individuals should adopt themselves to reduce disease risks. Third, examine the instruments currently at our disposal and push forward the development of mature technologies to be progressively implemented. Fourth, stimulate model analysis to evaluate cost-implications and cost-benefit equations.

Admittedly, prevention of GI disease is particularly complicated, relatively to other body systems, by the great diversity of organs, functions, control mechanisms and tissue biologies of the human digestive tract. Indeed, genetic, infections, immune, ischemic, metabolic and neoplastic etiologies should be considered, often in combination. Individuals themselves become major players, influencing disease development probabilities through their habits such as smoking, alcohol and drugs consumption, nutritional behaviour, exercise practice and risk exposure in general. Fortunately, prevention instruments at our disposal are already substantial, constantly expanding and improving. Of these instruments, however, we have certain categories, including imaging, endoscopy, histology that are relatively crude and/or invasive. They are likely to be gradually phased out in favour of secretion (blood, urine, feces) analysis better suited for mass screening, with lower cost and yatrogenic risks and greater precision. But, I would contend that mass application of genetic profiling will provide the most significant leap forward. The advent of personalized medicine will have profound and positive implications for GI disease prevention by identifying particular individual risks and facilitating the application of targeted preventive measures.

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POSTER ABSTRACTS

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Lifestyle factors influence heartburn and GERD rate in urban population

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Introduction: According to Montreal consensus (2005), the presence of a heartburn and/or regurgitation with a frequency once a week and more is considered to be GERD criteria. The objective of our work was to estimate the prevalence of main GERD symptoms: heartburn and regurgitation and to reveal medications used by patients for GERD treatment.

Methods: 908 people were included in a study (m – 347, f – 561, 15–87 years old). Respondents were offered to answer questions concerning the influence of lifestyle on GERD symptoms.

Results: Results of questioning revealed that the incidence of heartburn among studied population was 56.83%; prevalence of heartburn among men and women differed (59.65% and 55.1%, respectively). Incidental heartburn (less frequent than once a week) was revealed in 244 persons (26.87%), frequent heartburn corresponding to GERD symptoms (once a week and more often) – in 272 (29.95%) respondents. Prevalence of GERD increased with age of respondents starting from 12.82% (21–30 years old) and 20.67% (31–40 years old) up to 27.44%, 26.74% and 27.77% in age groups of 41–50, 51–60 and 61–70, respectively. In case of respondents older than 70 years old the incidence was even higher and goes up to 38%. Almost in all age groups GERD was revealed more often in men than women. Food intake was a major heartburn provoking factor: heartburn after meals appeared in 66.67% of persons; other factors had less influence on heartburn occurrence: fasting heartburn appeared in 15.5%, during the night period – in 14.34%, after physical activity – in 15.12%, after stress – in 8.91%, following inclinations – in 25.39% of cases. The role of all provoking factors, and first of all food intake, increased in patients with GERD.

Only 40.98% of persons with incidental heartburn and 76.84% GERD patients used medications. Meanwhile only 9.19% of persons with GERD took proton pump inhibitors, 4.8% – H₂-histamine blockers, 33.1% – used antacids for heartburn treatment.

Discussion/Conclusion:

1. Heartburn incidence by results of questioning was 56.83%, acidic regurgitation – 28.74%. GERD frequency was found to be 29.95%.
2. 76.84% of GERD patients took medications, however, only 14% of them took rational treatment with antisecretory drugs.

2

Differentiation of *H. pylori* pathogenicity factors and apoptosis association in gastric mucosa in genetically diverse populations

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Introduction: The aim was to study the relationship of *H. pylori* dissemination density (DD) and CagA strains with apoptosis in gastric mucosa in chronic gastritis in Mongoloids and Europoids of Eastern Siberia.

Methods: 22 adult Evenks and 24 Europoids were included. All subjects underwent upper digestive tract endoscopy and antrum mucosa biopsy specimens were taken. *H. pylori* were determined by histological methods; IgG to *H. pylori* and CagA strains were established by ELISA method. Apoptotic index in gastric mucosa was determined using TUNEL-method.

Results: The apoptotic index (AI) in gastric antrum mucosa was 5.19% in Europoids, 4.04% in Evenks ($p = 0.001$); in gastric corpus – 4.99%, and 3.19%, respectively, $p < 0.001$. DD correlated with the AI in antrum ($r = +0.80$; $p < 0.001$) and corpus ($r = +0.84$; $p < 0.001$) in greater degree in Europoids, than in Evenks ($r = +0.38$, $p = 0.03$; $r = +0.24$; $p = 0.18$). AI in antrum mucosa was higher in patients with CagA strains in comparison to persons without CagA in both populations. In gastric body apoptosis was increased in patients with CagA *H. pylori* in Evenks in greater degree than in aliens.

Conclusion: We have found different levels of the relationship of *H. pylori* dissemination density (DD) and CagA strains with apoptosis in gastric mucosa in chronic gastritis in Mongoloids and Europoids of Eastern Siberia.

Indolent gastric lymphoma

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Introduction: Extranodal marginal zone B-cell lymphoma of MALT type (E-MZL) is an indolent lymphoma comprised of heterogeneous small B-cells, including marginal zone (centrocyte-like) cells, monocytoid cells, and small lymphocytes in varying proportions.

Methods: During the last 18 years, there were registered 11 lesions of E-MZL, 1 follicular and 2 mantle cell lymphoma with primary gastric involvement.

Results: The most common presenting symptoms include: epigastric pain or discomfort 63,63%, anorexia 36,36%, weight loss 45,45%, nausea and/or vomiting 36,36%, occult gastrointestinal bleeding 27,27%, early satiety 45,45%. They typically occur in middle-aged men: median age 54,56%, and 63,63% was male. The lymphoid lesions were of unique determination except one case, which was initially diagnosed as a thyroid lymphoma with large cell. 63,63% of the cases are localized stage (IE/IIIE). Findings on upper endoscopy are: a mass or polypoid lesion with 27,27% or without ulceration 36,36%, benign-appearing gastric ulcer 18,18% nodularity thickened, cerebroid gastric folds 18,18%. The extension of a lesion across the pylorus into the duodenum is present in 18,18%, and is highly suggestive of lymphoma. The histology was classical excepting one case with E-MLZ lymphoma who presented significant plasmatic differentiation. This case presented at diagnosis a little monoclonal IgA peak (2.3 g/dl) which disappeared after gastric resection, undergone for diagnostic/therapeutically purpose. Diagnostic testing for *Helicobacter pylori* was made by urease methods, in association with endoscopy in 54,54% cases. It was positive in five of six cases tested.

Discussion/Conclusion: Primary gastric indolent lymphoma is rare, but the diagnosis is important because it has distinct prognosis and management from other malignant gastric lesions.

4

Indolent gastric lymphoma – Therapeutical options

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Introduction: Gastrointestinal NHLs are rare lesions and their optimal treatments have not been defined. The treatment of gastric extranodal marginal zone B-cell lymphoma of MALT type is dictated primarily by stage and histologic grade.

Methods: During the last 17 years, there were registered 19 lesions of E-MZL with gastric determinations.

Results: From the eleven cases with E-MZL gastric, six (54, 54%) present themselves in localized stage, IE, IIE. five of these ones (83, 33%) responded the Helicobacter pylori (HP) eradication therapy. In evolution, two patients relapsed, one locally and the other systemic. Both cases responded to CVP chemotherapy, the estimated survival rate of 5 years being 100%. Five patients (45,45%) presented with an advanced stage of the disease (III and IV), 18,18% has laparotomy for diagnostic/treatment reason, with partial gastric resection. Three of the five of advanced stage patients underwent eradication therapy for HP, but only one patient presented a partial response. A whole lot of patients who was in an advanced stage were treated with protocols of CVP or CHOP type by rapport of the presence of confluent clusters or sheets of large cells resembling centroblasts. The rate of response was 80%. Three of these patients presented multiple relapses, controlled by chemotherapy. The estimated survival rate of 5 years in this lot has been of 60%. For follicular lymphoma the treatment was R-CHOP or R-FC with rapid favourable evolution and the same as first line therapy for mantle cell lymphoma

Discussion/Conclusion: The E-MZL therapy presents characteristics through the response to the HP eradication therapy. For other type of gastric indolent B lymphoma mainly in advanced stage the first line therapy was polychemotherapy. The evolution and therapy of this lymphoproliferative lesions, besides these characteristics, is similar to the malignant indolent lymphomas.

The evolution of the esophageal cancer in Transylvania

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Introduction: Esophageal cancer is among the ten most prevalent malignancies and is the sixth leading cause of cancer deaths worldwide. In the world, especially in the western-European countries and US, the incidence of the esophageal cancer is increasing compared with the incidence of the gastric cancer. But the incidence of the cardia gastric cancer is increasing dramatically. This fact led to the new classification of the gastric cancer in non-cardia gastric cancer and cardia cancer.

The study is a follow-up of the changes in the prevalence of esophageal and gastric cancer in our region from Transylvania, the age and gender distribution.

Methods: We followed-up the evolution of the malignant lesions upon the last 10 years. There were 779 patients diagnosed with malignant tumours. All the patients underwent upper digestive endoscopy and biopsies were taken. Chromoendoscopy and magnifying endoscopy were also used.

Results: In the last 10 years there were diagnosed 779 patients with esophageal and gastric cancer. From these 182 were esophageal cancers and 597 gastric cancers. In the last 5 years the non-cardia gastric cancer is decreasing in incidence with 12.75%. The incidence of the lower esophageal cancer is increasing with 5.44% and cardia cancer increased with 12.77% in this period. There were no statistically significant differences between the age and gender of the patients. The morbidity of the esophageal cancer increased from 34 cases in 2005 to 106 cases in 2009 and the mortality increased from 25 cases in 2005 to 38 cases in 2009.

Discussion/Conclusion: The incidence of the esophageal cancer is increasing in our region. The incidence of the lower esophageal cancer and cardia cancer are increasing statistically significant in the past 10 years, with 5.44% and 12.77%, $p < 0.05$. These changes are correlating with the evolution of the esophageal and gastric cancer in the western european countries and in the world.

Expression of Toll-like receptors in children with abdominal pain and healthy infected with *Helicobacter pylori*

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Introduction: *Helicobacter pylori* (Hp) is acquired in childhood remain chronically in the gastric mucosa. The infection at this stage is clinically important because it can cause gastrointestinal illness in adults. Toll-like receptors (TLR) are involved in the recognition of molecular patterns and lipoprotein (TLR2), LPS (TLR4) and flagellin (TLR5). At the time, no one knows the level of expression of TLR in the Hp infection in children.

Methods: We collected blood and gastric biopsies from children with abdominal pain, and blood of 26 healthy children. Mononuclear cells were separated from blood and the expression level of the TLR's was evaluated by means of PCR real time, the biopsies were used for immunohistochemistry.

Results: Quantification by PCR real time of children with abdominal pain was (TLR2 Hp+ 2.47 ± 0.22 vs. Hp- 3.67 ± 0.39 , $p = 0.06$), (TLR4 Hp+ 3.08 ± 0.07 vs. Hp- 5.63 ± 0.42 , $p = 0.08$), (TLR5 Hp+ 2.81 ± 0.76 vs Hp- 4.76 ± 0.30 , $p = 0.17$). The results by immunohistochemistry were quantified as area/density in 200 μm of tissue (TLR2 Hp+ 1843 ± 1777 ; Hp- 3435 ± 1021 , $p = 0.036$), (TLR4 Hp+ 3878 ± 3700 ; Hp- 886 ± 970 , $p = 0.027$), (TLR5 Hp+ 4507 ± 3658 ; Hp- 1864 ± 1574 , $p = 0.04$).

While in asymptomatic children, the levels of expression in mononuclear cells were (TLR2 Hp+ 5.85 ± 0.72 vs. Hp- 6.49 ± 1.56 , $p = 0.06$), (TLR4 Hp+ 5.90 ± 0.62 vs. Hp- 7.49 ± 0.27 , $p = 0.08$), (TLR5 Hp+ 7.99 ± 1.14 vs. Hp- 7.47 ± 1.34 , $p = 0.17$).

Discussion/Conclusion: These results suggested that Hp is recognized by TLR5, however downregulated the expression of TLR2 and TLR4, which could have favoured the persistence of infection in adult life and contributing to the development of gastroduodenal disease. Similar expression of TLRs occurred in both gastric mucosa and blood, could be used as a marker for diagnosis of inflammation.

Máximo 250 palabras, enviar antes del 31 de Mayo, simposio 176

Duodenal eosinophilia and *Helicobacter pylori* infection in children with dyspepsia

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Background: It is suggested that both eosinophils and mast cells of the mucosal layer of the digestive tract have been implicated in the generation of abdominal pain, whereas the presence of *Helicobacter pylori* (*H. pylori*) in gastric epithelium is believed to be an essential step in the induction of active chronic inflammation of the gastroduodenal mucosa. The aim of this retrospective study was to determine eosinophil counts in duodenal mucosa in children with *H. pylori* infection who presented with dyspepsia.

Material and methods: A total of 1307 patients (aged 1–19 years) with functional dyspepsia undergoing an upper gastrointestinal (UGI) endoscopy were evaluated. All patients had minimum of 2 forceps biopsies obtained from the esophagus, gastric cardia, corpus, antrum, duodenal bulb and second portion of the duodenum. Routine histological evaluation (H,E staining) and Giemsa staining (to examine the presence of *H. pylori* infection) were performed. Gastric histopathology was defined and graded according to the Update Sydney System. Eosinophil counts were determined in the lamina propria, in the surface epithelium and crypt epithelium in each of the high-power fields (hpf) of the duodenal bioptates.

Results: Of 1307 patients who underwent UGI endoscopy, *H. pylori* was positive in 223 cases (17%): 83 boys, 140 girls; 40 cases in the age range of 1–10 years, 183 cases > 10 years of age). In the vast majority of children, *H. pylori*-positive gastritis was concomitant with essential duodenal lesions. Duodenal abnormalities presented as moderate to severe duodenitis manifested by increased cellularity of the lamina propria (by heavy infiltration mainly of lymphocytes, plasmocytes and granulocytes) and epithelial damage, frequently accompanied by superficial erosions. Duodenal biopsies showed an increase in mucosal eosinophils in 130 children with positive *H. pylori* positive-gastritis. The eosinophil counts of 1–5/hpf was found in 87 children (in 38 boys and 49 girls; in 72 cases > 10 years of age); 6–10 /hpf in 31 children (in 9 boys and 22 girls; in 25 cases > 10 r.ż.); > 10 eosinophils/hpf in 3 girls in the age range of 1–10 years. Sometimes duodenal eosinophilia coexisted with lymphonodular hyperplasia and with slight shortening of some intestinal villi.

Conclusion: The results indicate a distinct correlation between *H. pylori*-positive gastritis and mild duodenal mucosal eosinophilia in pediatric patients with dyspepsia.

***Helicobacter pylori* genotypes influence on gastric mucosa in patients with duodenal ulcer**

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Introduction: *Helicobacter pylori* (*H. pylori*) colonizes approximately two-thirds of the world's population. *H. pylori* infection plays a crucial role in the pathogenesis of chronic active gastritis, peptic ulcer and gastric cancer. The aim of the research was to study the influence of *H. pylori* genotypes on the morphological changes of gastric mucosa in patients with duodenal ulcer.

Methods: We examined 203 patients with duodenal ulcer at the age of 20–60 years, mean age was 40.0 ± 10.2 years. All patients underwent upper endoscopy with target biopsy. For polymerase chain reaction брались biopsy specimens from antral part of the stomach were taken. *H. pylori* genes *cagA*, *vacA* m1, *vacA* m2, *vacA* s1, *vacA* s2, *iceA1*, *iceA2*, *babA* and *dupA* (*jhp0917* + *jhp0918*) were determined. For morphological investigation two biopsy specimens were taken from the middle of the antral part of the stomach and two – from the middle of the body of the stomach.

Results: In patients with duodenal ulcer with high activity (2–3 points) in gastric mucosa of the antral part of the stomach *H. pylori* gene *babA* was determined more often than in those with low activity (0–1 points) ($p = 0.039$). The occurrence rate of *vacAm1* genotype of vacuolating cytotoxin gene prevails in the group of patients with more severe inflammation (2–3 points) in gastric corpus mucosa ($p = 0.033$), but in patients with less severe inflammation (0–1 points) *vacAm2* genotype was determined more often ($p = 0.015$). A larger number of lymphoid follicles was associated with *jhp0918* gene ($p = 0.033$). When atrophy in gastric corpus mucosa was more clearly marked (2-3 points) *jhp0917* ($p = 0.038$) и *dupA* ($p = 0.011$) genes were determined more often.

Discussion/Conclusion: Thus *H. pylori* genotypes influence on morphological parameters of gastric mucosa was ascertained.

Smoking may contribute to development of gastric cancer in young Turkish man without family history

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Introduction: Besides precursor lesions such as atrophic gastritis and intestinal metaplasia, familial predisposition, dietary and lifestyle factors such as tobacco smoking may also play a role in gastric cancer development. The aim of this study was to evaluate factors that may have an effect in the development of gastric cancer.

Method: Three hundred and ninety-nine gastric cancer patients of whom the median age was 59.0 ± 13.0 (range: 25–87) years, followed at a single cancer center between 2005 and 2009 involved in this study. Data was collected retrospectively from the medical records.

Results: Male/female ratio was 2.4 (282 man and 117 women). Co-morbidities including diabetes mellitus, hypertension, coronary artery disease, renal failure, benign gastric disease, family history of gastric cancer, stage and location of the gastric cancer were not different between patients after grouping according to the age and sex. However tobacco smoking was more common in men than in women (136 men vs. 7 women, $p < 0.001$). Mean package/year of cigarette was 42.46 ± 22.3 . We found that after sub-grouping of men according to age, greater number of younger men (equal or less than 55 years of age) smoked tobacco compared to older men (61.7% vs. 40.6%, $p = 0.001$). This difference was more prominent in younger men without family history than the older men with family history of gastric cancer in their first relatives (60.9% vs. 40.0%, $p = 0.002$). There were no difference in smoking habits according to age and family history in women possibly because of small number of women smoking tobacco.

Discussion: Relationship between smoking and gastric cancer may play a role in early development of gastric cancer. Further studies are needed to identify characteristics of these high risk patients.

Is stress, anxiety and personality playing a role in the etiology of peptic ulcer

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Introduction: Peptic ulcer (PU) is a common finding in young, active people. The aim of this study is to establish the role of the personality and the importance of stress in young patients with PU.

Methods: The study was carried out in a group of 44 patients diagnosed with PU, hospitalized in the IVth Medical Clinic of the University of Medicine and Pharmacy "V. Babes" Timisoara, in a 12 months period. The patients were aged between 19–43 years; the mean age of those patients was 31 years. Of them 23 were women and 21 were men. We applied in all patients a psychological test for personality (E.P.Q.), and a stress and anxiety test.

Results: Stress was present in all patients. In 27.3% of patients, the stress was very high, in 54.5% of patients stress was medium and in 18.2% the stress was normal but not absent. From the 44 patients 32 patients had an introverted personality and 12 had an extraverted personality. Anxiety was a symptom in 23 patients out of the 44.

Discussion/Conclusion: Stress and anxiety seems to play a role in the etiology of the PU; stress was present in all patients and anxiety was present in 52.3% of the patients. Most of the patients (72.7%) included in the study were introverts.

Heavy smoking as a risk factor of *Helicobacter pylori* eradication failure

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Introduction: The aim of this study was to estimate the efficacy of *Helicobacter pylori* (*H. pylori*) eradication in the region with high prevalence of the infection among patients who were heavy or moderate smokers and non-smokers.

Methods: A total of 169 patients with *H. pylori*-associated peptic ulcer received eradication therapy according to Maastricht-3 Consensus Report. All patients were divided into 4 groups. The first group included patients who smoked more than 20 cigarettes per day (29 patients), the second group was made up of those who smoked 10–20 cigarettes per day (34 patients), the third group consisted of the patients who smoked less than 10 cigarettes per day (14 patients) and the fourth group included 92 non-smoking patients.

Results: On the whole 101 patients had successful eradication. Failed eradication was observed in 68 patients. Among patients of the first group eradication was successful in 11 cases (16.2%), in the second, the third and the fourth groups successful results were achieved in 18 cases (52.9%), 11 cases (78.6%) and 61 cases (66.3%), respectively. There were significant differences in eradication frequencies among heavy smokers and non-smokers (chi-square = 6.03; $p = 0.014$; OR = 3.17; 95% CI: 1.33–7.53), but there were no differences among heavy smokers and moderate smokers (the second or the third groups) as well as among moderate smokers and non-smokers (the fourth group).

Discussion/Conclusion: Eradication therapy failure in the population with high prevalence of *H. pylori* infection occurs more often among heavy smokers.

Lifestyle risk factors and relationship with gastroesophageal reflux disease

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Introduction: Gastroesophageal reflux disease (GERD) is quite common and often goes undiagnosed because of the atypical symptoms. Studies indicated that gastroesophageal reflux disease (GERD) is associated with obesity, smoking, esophagitis, diet, and lifestyle. The purpose of this study was to reveal our experience from our clinic in the diagnosis of GERD and the risk factors associated with GERD in our region.

Methods: The study comprised 383 patients (63% male, mean age 53 ± 12 years) diagnosed with GERD that were hospitalised in The IVth Medical Clinic of University of Medicine and Pharmacy Victor Babes, Timisoara, during the last three years. GERD was defined as heartburn and/or regurgitation of any frequency during the previous week. All the patients were investigated clinically, paraclinically and upper gastrointestinal endoscopy was performed.

Results: By all the patients, 89% were heavy drinkers, 73% were smokers and 68% of them had a diet rich in fatty foods, spicy foods, chocolate, caffeine, onions, tomato, sauce, carbonated beverages, mint. 69% of them were with obesity, 34% of them were overweight and 7% of them were with normal weight. At upper gastrointestinal endoscopy could be visualised: grade A and B reflux esophagitis in 39% of cases and Barrett's esophagus in 15% of cases.

Discussion/Conclusion: Our data revealed that alcohol consumption, smoking and inadequate meals tend to be associated with an increased risk of erosive esophagitis and Barrett's esophagus. Lifestyle changes for management of GERD include dietary modification, weight reduction, avoidance of alcohol, and smoking cessation.

Gastric cancer incidence in Russian Federation

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Introduction: The aim of our research was to analyze gastric cancer and atrophic gastritis incidence and risk factors in population of Russian Federation.

Methods: We have analyzed the reported data on incidence and risk factors of gastric cancer among the population of various regions of Russia. The large epidemiological study of atrophic gastritis in adult persons in Tyva, Khakassia and Evenkia was performed. Upper digestive tract endoscopy and identification of *H. pylori* were done in 3494 patients. Morphological study of gastric mucosa was carried in 759 patients.

Results: The gastric cancer incidence in Russian population in different regions varies about 30 per 100,000, reaching maximum (50–60 per 100,000) in Mongoloids in the North of European part of Russia, in Tuva and Buryatia (Siberia). The prevalence of *H. pylori* in urban and rural population of Russia varies about 80–90%. About 80% of men smoke tobacco in Russia. About 50% of the Russian population use salted fish, pickled vegetables and strong alcoholic beverage systematically. The prevalence of atrophic gastritis in different ethnic groups of Siberia was correlated with gastric cancer incidence.

Conclusion: The relationship of high prevalence of risk factors and gastric cancer high incidence in the population of the Russian Federation was registered.

The pathogenesis of anemia in inflammatory bowel disease

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Introduction: The pathogenesis of the anaemic syndrome in inflammatory bowel disease (IBD) is complex. It can be generated by the chronic inflammation, by the repeated blood loss, by the malabsorption of the folic acid and B₁₂ vitamin. Besides, the anaemia may preexist at the debut of the intestinal disease.

Material and method: We have evaluated a number of 54 patients with IBD during a period of 8 years, out of which 34 were diagnosed with ulcerative colitis (UC) and 20 with the Crohn's disease (CD). It was determined the Ht value, Hb red cell indices, the number of reticulocytes, the total capacity of iron bounding (CTLF), the latent capacity of iron bounding (CLLF), the transferrin saturation (TS), the ferritin and reactive C proteine.

Results: Out of these ones, 17 of the patients with UC and 9 with CB presented anaemia (Hb under 13.5 g/dl in men and under 11.5 g/dl in women). The medium Hb value in the lot of patients with anaemia was of 8.3 ± 1.6 and Ht value was of 28 ± 3.5 . In 11 of 18 anaemic patients ($\chi^2 = 3.51$, $p < 0.055$), the intestinal disease was active. In 5 of 7 patients with anaemia without active disease, the investigations and the epidemiologic study suggests an associated cause of the anaemia (iron deficiency). In one case, the red cell indices suggest macrocytosis and anaemia is remitted after treatment with folic acid and B₁₂ vitamin.

Discussion/Conclusion: The anaemia follows frequently IBD in 37.75% percentage. The increased prevalence of the anaemia in IBD may be justified in a way by the local socioeconomic conditions. The anemia is also correlated with the activity degree of the disease.

The numerical and functional alterations of platelets in inflammatory bowel disease

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Introduction: The pathogenesis of platelets abnormality in inflammatory bowel disease (IBD) is complex. It can be generated by the chronic inflammation, by the repeated blood loss, by the therapy, malabsorption of the folic acid and B₁₂ vitamin.

Methods: We studied a lot of 44 patients with IBD (26 patients with ulcerative colitis (UC) and 16 with Crohn's disease (CD) during a period of 5 years.

Results: The thrombocytosis is present in a percentage of 30.95% from the whole lot (31.25% patients with CD and 30.76% with UC). Patients with CD presented higher values of the platelets number 687,000/mm² versus 467,000/mm² ($\chi^2 = 2.35$, $p < 0.05$). A patient was initially considered as having reactive thrombocytosis, in time being developed manifestations and suggestive complications for the essential thrombocytemia. The thrombocytosis is correlated with the CRP value ($\chi^2 = 3.35$, $p < 0.05$) and less with the fibrinogen value ($\chi^2 = 3.20$, $p < 0.056$) and with the state activity of the disease ($\chi^2 = 3.42$, $p < 0.05$). The reactive C protein (CRP) is increased in all cases of thrombocytosis, correlating in a way with this one's degree. Thrombocytopenia is moderate between 50–100,000/mm² and was found in 5.6% especially in heavy treated patients.

Discussion/Conclusion: The thrombocytosis is present in approximately 1/3 of the IBD cases. The thrombocytosis values can get to values that can raise problems of differentiated diagnosis, but the presence of the digestive disease and the evolution clarified it.

Gluten-free diet adherent: But at what cost? *Lifestyle challenges & quality of life in celiac disease*

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Introduction: The gluten-free diet (GFD) is the mainstay of treatment in Coeliac Disease (CD). There is very limited data surrounding lifestyle difficulties associated with the diet. The impact on quality of life (QoL) is debated. Uncertainty may stem from focusing on GFD adherence rather than the degree of difficulty encountered to achieve adherence. We hypothesised that the more difficult the coeliac individual perceives following a GFD, the lower their QoL will be.

Methods: Postal survey (n = 573) of histologically proven coeliac individuals (n = 225) and age and sex matched controls (n = 348). Questionnaire included the SF-36 QoL measure, The Hospital Anxiety & Depression scale and an assessment of GFD living.

Results: Around two thirds of CD respondents reported full GFD adherence (always: 64.6%). Lifestyle obstacles encountered included eating out (88%), vocational (27%) homelife (12%), travelling (73%), personal relationships (13%), socialising (71%). Perceived GFD difficulty reported as no difficulty (20%), sometimes (61%), mostly difficult (14%), impossible (5%). Stepwise reductions in QoL scores were observed based on increasing levels of difficulty following the GFD ($p \leq 0.0001$). Furthermore, median HADS scores suggest that finding the GFD 'mostly difficult' is associated with possible anxiety and probable depression ($p \leq 0.0001$).

Table: Comparison of SF-36 and HADS scores based on degree of GFD difficulty reported

	Controls	No difficulty	Sometimes difficult	Mostly difficult	Impossible	Significance
SF-36 PCS (Median)	53.40	49.07	47.38	39.49	35.50	$p > 0.05$
SF-36 MCS (Median)	50.77	52.39	44.61	38.72	31.47	$p < 0.0001$
HADS-A (Median)	5.3	4	7	9	7	$p < 0.0001$
HADS-D (Median)	5.5	5	7	11	8	$p < 0.0001$

SF-36 PCS: Physical component summary; **SF-36 MCS:** Mental component summary; **HADS-A:** HADS Anxiety Subscale; **HADS-D:** HADS Depression Subscale

Discussion/Conclusion: A variety of lifestyle obstacles are associated with GFD living and leading to difficulty achieving dietary adherence. This difficulty has a negative impact on patient wellbeing. Future investigators must consider QoL in the context of GFD difficulty in addition to adherence and clinicians must appreciate the impact this restrictive diet has on the lifestyle of the CD individual and the negative impact this has on their self-reported QoL.

Note to editor: This abstract is 245 words long excluding the table. This poster was presented at The British Society of Gastroenterology Annual Meeting on March 25th, 2010.

Comparing quality of life in celiac disease and inflammatory bowel disease: A paradigm shift in our perceptions?

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Introduction: The SF-36 is a valid and reliable quality of life (QoL) measure in celiac disease (CD) and inflammatory bowel disease (IBD). However, there has never been a study to compare the QoL in these two diseases. We hypothesised that individuals with IBD report a worse QoL than those with CD because IBD is considered the more severe disease of the two.

Methods: Postal survey (n = 1031): histologically proven CD (n = 225), Crohn's disease (n = 230) and ulcerative colitis (UC) (n = 228) compared with age and sex matched controls (n = 348). Questionnaire included SF-36, Hospital Anxiety and Depression Scale, ROME II criteria and reflux oesophagitis (RO) screen. Disease-specific assessment: Harvey-Bradshaw Index (HBI), Simple Colitis Activity Index (SCAI) or assessment of gluten-free diet (GFD) adherence.

Results: Disease duration had a negligible impact on QoL. At least one RO symptom was reported by 66% of CD respondents, 72% of Crohn's, 62% of UC and 50% of controls. Stepwise reductions in SF-36 and increases in HADS-A and HADS-D scores with increasing RO symptom severity was observed ($p \leq 0.05$). 22% of CD respondents, 24% of CD, 16% of UC and 6% of controls met ROME II criteria for IBS further reducing QoL in all groups ($p \leq 0.0001$).

Overall Group Comparison of SF-36 and HADS Scores

	Crohn's Disease	Ulcerative Colitis	Celiac Disease	Controls	p Value
SF-36 PCS (Median)	43.09	49.19	46.99	53.40	< 0.0001
SF-36 MCS (Median)	42.90	50.65	46.10	50.77	< 0.0001
HADS-A (Median)	8.0	6.0	7.3	5.3	< 0.0001
HADS-D (Median)	9.0	7.0	7.5	5.5	< 0.0001

Discussion/Conclusion: This is the first study to report a comparison of QoL in two major chronic inflammatory GI diseases. Surprisingly, celiac patients report a worse QoL and increased risk of anxiety and depression than UC patients ($p \leq 0.0001$). In addition we observed that GI motor abnormalities are more common in the disease groups and further reduce patient wellbeing.

Note to editor: This abstract is 250 words long excluding the table. This poster was presented at The British Society of Gastroenterology Annual Meeting on March 25th, 2010.

Prevalence of Crohn's disease among the patients with infectious diarrheal diseases

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Introduction: Gastrointestinal diseases are still the prevailing component of the infectious pathology in our country. The onset of Crohn's disease in most of the patients is usually misdiagnosed with infectious diarrhea.

Aim: To determine the prevalence of Crohn's disease among the patients with infectious diarrheal diseases, separated by etiologic specificity and the pathogenicity of the infectious agents in a cohort of patients, admitted with relevant symptoms.

Methods: 13,307 patients were treated in the University Clinic of Infectious Diseases in Plovdiv for 7-year period (2003–2009). For the whole period five patients with new found Crohn's disease were diagnosed by using instrumental, histological, clinical and laboratory methods.

Results: The most frequently isolated bacterial pathogens were Salmonella spp. in 394 (2.96%) cases, Shigella spp. in 302 (2.27%), EEC strains in 220 (1.65%), Staphylococcus strains in 36 (0.27%), Proteus strains in 12 (0.09%) and Pseudomonas in 3 (0.02%). Five patients or 0.04% were proven to be Crohn's disease.

Discussion/Conclusion: The prevalence of Crohn's disease among patients with infectious diarrheal diseases in Plovdiv region is 0.13% compared to 0.18% total Crohn's disease prevalence in the whole country. The high rate of prevalence of Crohn's disease among the patients with infectious diarrheal diseases in the clinics of infectious diseases proves that these centres could be the possible choice for an early screening of such patients.

Changes in the expression of cellular iron transport machinery occur in pre-neoplastic lesions within the colon in both sporadic and familial polyposis

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Introduction: Sporadic colorectal adenocarcinoma (CRC) develops through the adenoma-carcinoma sequence involving in the tumour suppressor gene adenomatous polyposis coli (APC). Familial adenomatous polyposis coli (FAP) is a condition in which germline mutations in APC lead to early adenoma and tumour formation. Mutations in APC lead to increased Wnt signalling, the main oncogenic pathway in colon cancer, upregulating c-myc. Increased expression of the cellular iron import proteins (TfR1 and DMT-1) are found in CRC, and lead to increased intracellular iron. The aim of this study is to determine whether these changes can be found in pre-cancerous adenomatous polyps in sporadic and familial adenomatous polyposis.

Methods: Colonic tissue from i) sporadic adenomas (n = 15) and ii) familial adenomatous polyposis coli (n = 10) was collected with matched normal colon. Real Time PCR was used to determine the expression of the iron transport proteins (TFR1, DMT1, ferroportin and ferritin) and c-myc.

Results: Sporadic and familial adenomatous tissue showed a significant fold increase in TfR1, DMT1 and c-myc expression in 15/25, 16/25 and 14/25 tissue samples respectively. Furthermore both TfR1 and DMT1 were tightly correlated with c-myc expression ($R^2 > 0.94$ and 0.81 respectively).

Discussion/Conclusion: This study demonstrates that changes in the expression of iron transport machinery occur in the pre-cancerous adenomatous polyps in both sporadic and familial polyposis and may be regulated by the oncogene c-myc.

Infestation with *Giardia duodenalis* – A study of parasitary duodenitis

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Introduction: The aim of this abstract is to evaluate the prevalence of the infestation with *Giardia duodenalis* among the hospitalized patients from Southern Transylvania and to analyze the duodenal inflammation determined by this parasitosis.

Methods: The epidemiological study was performed on a group of 889 consecutive hospitalized patients and the diagnosis of *Giardia lamblia* parasitosis was established by the presence of lamblic cysts in a stool sample. At a number of 30 symptomatic patients there was also analyzed the histological aspect of the duodenal biopsy samples. The patients were divided into 3 groups, according to the etiology of the duodenitis: group A – *Lamblia* (10 patients), group B – *Helicobacter pylori* (10 patients) and group C – association between *Lamblia* and *Helicobacter pylori* (10 patients). The patients with gastric ulcer, duodenal ulcer and gastric cancer were excluded from the study.

Results: Among the 889 patients (381 men and 508 women with the age between 19 and 82), a number of 649 patients (73%) were diagnosed with lamblia. 442 patients (68.10%) with lamblia had symptoms related with this parasitosis. The histological exam showed, at 8 from the 10 patients from group A, moderate flattening of the villosity and an increased number of lymphocytes in lamina propria. In group B, there was predominance (7 out of 10 patients) of the superficial duodenitis with gastric metaplasia. In group C, the dominant aspect was of interstitial duodenitis and flattening villosities.

Discussion/Conclusion: At the population from the studied geographical area there is an important interrelation with *Giardia duodenalis*. At 31.9% from the patients, the parasitosis was asymptomatic. The association between lamblia – infection with *Helicobacter pylori* determines a more severe duodenitis than the cumulative histological aspect of the two etiologies.

IBD and IBS: Some aspects of pathogenesis

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The phases of the endointoxication were discovered for children with IBD-C and IBS. There were observed five phases.

Introduction: Pediatric IBD includes three diseases of unknown causation: UC, which affects only the large bowel; CD, which can affect the entire gastrointestinal tract; and, indeterminate colitis, which consists of large bowel inflammation that shows elements of both CD and UC. IBS is a functional bowel disorder characterized by chronic abdominal pain, discomfort, diarrhea or constipation, or they may alternate (classified as IBS-D, IBS-C or IBS-A, respectively). Some children with IBD also have IBS. IBS is a common source of symptoms refractory to treatment in IBD. Pain is the too often neglected symptom of Pediatric IBD and the dominant symptom of Pediatric IBS.

Methods: We estimated quantitative and qualitative changes of metabolic status in accordance with LMMWP (low and medium molecular weight peptides – universal markers of intoxications) and OP (oligopeptides), defined in erythrocytes, plasma and urine.

Results: 135 children with IBS-C and 40 with IBD were examined. In the initial phase of intoxications, the increase of LMMWP only on erythrocytes is observed. In the second phase, the moderate increase of concentration of LMMWP in plasma and on erythrocytes is observed (a phase of accumulation of products from the center of aggression). In the third phase LMMWP on erythrocytes remains constant (a phase of full saturation), and in plasma concentration continues to accrue, reaching significant sizes. The fourth phase is characterized by decrease LMMWP on erythrocytes (probable changes of structure of membranes) and growth of maintenance LMMWP in plasma (a phase of an inconsistency of systems of a homeostasis). The fifth, terminal phase, is characterized by significant damage of the membranes, accompanied decrease LMMWP both on erythrocytes, and in plasma (full decompensation).

Discussion/Conclusion: Enhanced injured surface in IBD and coprostasis in IBS-C contributes to auspicious conditions for bacterium and toxin penetration in blood flow. The most prominent endointoxication was observed in children with total UC. On the base of these findings we calculated the adequate dose of enterosorbents.

Lifestyle factors and IBD

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The phases of the endointoxication were discovered for children with non-specific ulcer colitis. There were observed five phases.

Introduction: Enhanced injured surface at the non-specific ulcer colitis (especially for total affection of colon) contributes to auspicious conditions for bacterium and toxin penetration in blood flow. The endointoxication contributes to maintain and to progress of metabolic and immunological changes. It is accompanied by disturbance of regulating homeostasis system with the following disturbances of organs and systems of detoxication.

Methods: We estimated quantitative and qualitative changes of metabolic status in accordance with LMMWP (low and medium molecular weight peptides – universal markers of intoxications) and OP (oligopeptides), defined in erythrocytes, plasma and urine. Correlation between the extent of affection, expression of symptoms with the degree and the stage of endointoxication.

Results: In the initial phase, the increase of LMMWP only on erythrocytes is observed. In the second phase, the moderate increase of concentration of LMMWP in plasma and on erythrocytes is observed (a phase of accumulation of products from the center of aggression). In the third phase LMMWP on erythrocytes remains constant (a phase of full saturation), and in plasma concentration continues to accrue, reaching significant sizes. The fourth phase is characterized by decrease LMMWP on erythrocytes (probable changes of structure of membranes) and growth of maintenance LMMWP in plasma (a phase of an inconsistency of systems of a homeostasis). The fifth, terminal phase, is characterized by significant damage of the membranes, accompanied decrease LMMWP both on erythrocytes, and in plasma (full decompensation).

Discussion/Conclusion: The most prominent endointoxication was observed in children with extraintestinal manifestations the predominant of which was liver dysfunction. On the base of these findings we calculated the adequate dose of enterosorbents, used in a complex therapy of NUC.

Zinc and its role in IBD

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Deficiencies of trace elements are frequent in inflammatory bowel disease.

Introduction: Pediatric IBD includes UC, which affects only the large bowel; CD, which can affect the entire gastrointestinal tract.

Methods: 80 patients with Crohn's disease and ulcerative colitis were analyzed.

Results: Deficiencies were found in 81% of patients with Crohn's disease and ulcerative colitis, predominantly a deficiency of iron, of copper and of zinc. Zinc is an essential mineral that is naturally present in some foods, added to others, and available as a dietary supplement.

Zinc is involved in numerous aspects of cellular metabolism. It is required for the catalytic activity of approximately 100 enzymes and it plays a role in immune function, protein synthesis, wound healing, DNA synthesis, and cell division. Zinc also supports normal growth and development and is required for proper sense of taste and smell. A daily intake of zinc is required to maintain a steady state because the body has no specialized zinc storage system. Zinc deficiency is characterized by growth retardation, loss of appetite, and impaired immune function. In more severe cases, zinc deficiency causes hair loss, diarrhea, delayed sexual maturation, impotence, hypogonadism in males, and eye and skin lesions. Weight loss, delayed healing of wounds, taste abnormalities, and mental lethargy can also occur. Many of these symptoms are non-specific.

Discussion/Conclusion: In view of the high frequency of deficiencies in patients with inflammatory bowel disease it seems to be important to check frequently for extraintestinal complications.

Lipids and products of their peroxidation in blood plasma in conditions of stress-induced ulcer

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Annually in our country are about 1 million people with an ulcerous disease under a clinical supervision, frequency of annual relapses is 60–82%. Due to this data gastric ulceration is known to be an important problem of modern medicine.

The article is devoted to investigation of different types of lipids in rat blood under experimental ulceration. Results prove that in condition of stress model of ulcer violation of lipoperoxid homeostasis can take place. The action of ulcerogenic factors has a reflection on the level of universal integral system of organism – blood composition which reflects the pathological events in organism.

White non-linear rats were used in experiments. For the design of gastric ulcer was used the modified method of “immobilization stress”. Neutral lipids were fractionated with the method of TLC on the plates of “Sorbfil”. Catalytic activity in plasma of blood of rats was determined with a spectrofotometrical method.

In our experiments, the increasing of triglycerides and fatty acids levels was observed; meanwhile the content of cholesterol was invariable. The level of lipid peroxidation products was increased. In addition, catalase activity was decreased in 2.9 times.

For stress-induct gastric ulceration is characteristically an increase of content of Triacylglycerol, fatty acids, lipid peroxidation content and decrease of activity of catalase in plasma of blood. Indexes of lipid metabolism of plasma of blood are important in characterisation of the functional state of the metabolic systems of organism. Determination of their composition can be used as a diagnostic marker at different pathologies, including ulcerous disease.

Inflammatory bowel disease in Bangladeshis and Caucasians: Same or different?

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Introduction: The incidence of IBD in Asian ethnic minorities in the UK has risen in recent years. On the basis of our experience of looking after patients with IBD in E London, we have tested the hypotheses that, in comparison with the local Caucasian population, Bangladeshis with IBD (1) develop IBD at a younger age; (2) more often have Crohn's disease; and (3) have a more aggressive disease course.

Methods: We obtained clinical data from electronic patient records (EPR) of 262 consecutive patients (84 Bangladeshis, 178 Caucasians) attending IBD clinics during March-May 2010. To avoid risk of tertiary referral bias, we restricted our study groups to residents of local catchment area. We then matched 84 Bangladeshis to 84 Caucasians for age at diagnosis (22 [1.2] years (mean [SEM]) and disease duration (6.5 [0.5] years): data on phenotype (Montreal), disease course and treatment were again obtained.

Results: Amongst the 262 patients initially screened, only 3/84 Bangladeshis compared with 50/178 Caucasians had IBD diagnosed at age > 40 years ($p < 0.001$). There was no difference in the proportion of IBD diagnoses between the matched Bangladeshis (Crohn's: 55, UC: 25, colitis of uncertain type or etiology [CUTE]: 4) and Caucasians (Crohn's: 44, UC: 34, CUTE: 6). There were no differences in Montreal classification for either Crohn's or UC between Bangladeshis and Caucasians. There were more hospital admissions in the Bangladeshis (1 [0–15] (median [range]) than Caucasians ($p = 0.02$). More Bangladeshis with Crohn's had anti TNF therapy (22/55 [40%]) than did Caucasians (7/44 [16%]) ($p = 0.01$); a higher proportion of Bangladeshis had anti TNF therapy early in their disease course (Kaplan-Meier, log rank test $p < 0.01$). Serum Hb (12.7 [0.20] g/dl vs. 13.1 [0.18]; $p = 0.05$), MCV (82 [0.88] fl vs. 89 [0.79]; $p < 0.0001$) and vitamin D levels (34 [3.2] vs. 67 [6.4]; $p < 0.001$) were each lower in Bangladeshis than Caucasians.

Discussion/Conclusion: Few Bangladeshi patients are aged over 40 at diagnosis of IBD. Despite similar disease distribution and phenotype at diagnosis Bangladeshis have more hospital admissions; more often need anti TNF therapy, and need it earlier in their disease than Caucasians suggesting more aggressive disease. In view of the anti-inflammatory properties of vitamin D, it is conceivable that vitamin D deficiency may contribute to the apparently more aggressive course of Crohn's in Bangladeshi patients.

The effectiveness of high-dose iron treatment in patients with inflammatory bowel disease

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Introduction: Iron-deficiency anaemia is common in IBD, regardless of the activity of disease. For most, oral iron can be delivered easily and safely. Some however cannot tolerate it and have to resort to parenteral preparations. Previous dextran preparations were limited by severe adverse reactions, and have fallen out of favour.

Methods: We have used iron sucrose 200 mg (Venofer™) in 45 patients. While extremely well tolerated, there is a need for multiple infusions. This results in a complex process including many trips to hospital (range 3–87 visits). Ferric carboxymaltose (Ferinject™) can be given in larger dose in a single infusion (up to 1000 mg) with no reported risk of anaphylaxis, and thus for patients to receive high-dose intravenous iron with far fewer trips to hospital. The infusion time is reduced, with an average of 15 min (60 min with iron sucrose). 21 patients have now been treated with ferric carboxymaltose.

Results: For Venofer, the mean number of visits has been 11.8 over an average of 19.7 months. The mean cost per patient has been £235. For Ferinject, the average number of visits has been 2.5, over a mean time period of 7.3 months. The mean cost per patient has been £507.

Discussion/Conclusion: Our regular patients much prefer the new regime, with fewer visits to hospital. It is more responsive to their clinical needs, they can manage their time more easily, and fewer out-patient attendances have been needed. Advantages for the hospital include less nursing time, fewer appointments and quicker pharmacy processing. The extra cost of infusions (Ferinject™ £255 vs. Venofer™ £100 per 1000 mg) may be seen to be offset by these other advantages.

The effects of N-acetylcysteine and beta-glucan on acetic acid-induced colitis in rats

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Introduction and aim: Ulcerative colitis is a chronic recurrent inflammatory bowel disease in which oxidative stress has been implicated. N-acetylcysteine (NAC) and beta-glucan (BG) are anti-oxidant and also anti-inflammatory substances. The aim of the present study was to evaluate possible protective effects of NAC and BG against acetic acid-induced colitis in a rat model.

Materials and methods: In this study 50 male Wistar-Albino rats were used. Rats were administered intragastric saline (control group) or intrarectal acetic acid (colitis group). Rats with acetic acid-induced colitis were treated by intragastric gavage administration of N-acetylcysteine (NAC) (200 mg/kg), beta-glucan (BG) (100 mg/kg) and NAC + BG. NAC or BG received during 7 days. At the end of the study the distal 8 cm of the colon was removed. The degree of tissue injuries was assessed histopathological scores of the colonic mucosa. Malondialdehyde (MDA), myeloperoxidase (MPO), glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase (CAT) levels were measured in tissue extracts of the dissected colon.

Results: MDA and MPO levels were significantly low, SOD and CAT levels were significantly higher in monotherapy and combined therapy groups. This findings suggest that all treatment modalities have beneficial effect on inflammation that seen in colitis. Of treatment groups MDA and MPO levels were not significant. Gpx levels were highest among only NAC treated group. For other anti-oxidant enzymes (SOD, CAT), there were no difference between NAC and BG group, but in combination group anti-oxidant defence was lower than NAC group. Microscopic evaluation revealed that damage score was lowest in NAC group, but no statistical significance was found between treatment groups.

Conclusion: The results of this study suggest that NAC and/or BG treatment modalities have beneficial effect in colitis. But combined therapy compared with monotherapy did not show additional beneficial effect.

The insulin-like growth factor-I receptor, connexin 26 and antiapoptotic marker Bcl-xL in human colorectal cancer

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Introduction: Insulin-like growth factor (IGF) and its receptor (IGF-IR) play an important role in mitogenesis, apoptosis, growth and proliferation of several types of cancers. Overexpression of IGF-IR in colorectal cancer is associated with increase of cancer cells proliferation and migration as well as inhibition of apoptosis. In our previous reports we demonstrated correlations between IGF-IR and apoptosis. Moreover we observed relationships between connexin 26 (Cx26) expression and apoptotic markers in human colorectal cancer. Recently, it has been shown that expression of connexins and gap junction functions are also regulated by growth factors including IGF-I. Therefore, in this study we have focused on the relationships between IGF-IR and Cx26 as well as Bcl-xL expression.

Methods: A total number of 115 cases of colorectal cancer were examined by immunohistochemistry, using the avidin-biotin-peroxidase method. Associations among above proteins were assessed in the entire group of colorectal cancer patients and its subgroups depending on lymph node involvement (N0 and N1), histological grade (G2 and G3), extent of tumor growth (pT1 + pT2 and pT3 + pT4), histopathologic type (adenocarcinoma and mucinous carcinoma), sex, age (≤ 60 and > 60) and tumor site (colon and rectum).

Results: The expression of IGF-IR, Cx26 and Bcl-xL was noted in 47%, 56.5% and 75.6% of the tumors, respectively. In the entire group of patients we found the positive correlation between IGF-IR and Cx26 ($p < 0.0001$, $r = 0.374$) as well as between IGF-IR and Bcl-xL ($p < 0.0001$, $r = 0.344$).

Discussion/Conclusion: Our results may suggest that the insulin like growth system is involved in regulation of apoptosis and probably connexin expression in colorectal cancer cells.

Characterization of tumor infiltrating lymphocytes in colorectal cancer

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Introduction: Colorectal cancer represents the second leading cause of cancer-related mortality in developed countries. It is well established that different subpopulations of lymphocytes play an important role in the effector phase of immune response to neoplastic cells. The aim of the present study has been to evaluate sample subpopulations of lymphocytes within the primary tumor of colorectal cancer as well as in tissues surrounding the tumor and in a healthy intestine.

Methods: The research included 34 patients (15 females and 19 males), aged 45 to 78, operated on for adenocarcinoma of the large intestine. CD4⁺, CD8⁺, CD16⁺56⁺, CD4⁺CD25⁺ Foxp3⁺(T4reg) and CD8⁺CD25⁺Foxp3⁺(T8reg) lymphocytes from tumors were compared to lymphocytes from surrounding the tumor and normal mucosae. The evaluation was carried out in flow cytometer EPICS XL Coulter applying antibodies of BD Biosciences.

Results: Markedly higher mean values of proportion of CD4⁺ cells, CD4⁺/CD8⁺ CD4⁺CD25⁺Foxp3⁺ and CD8⁺CD25⁺Foxp3⁺ lymphocytes in tumors in regard to analogical values assessed in normal colonic mucosa have been found.

Discussion/Conclusion: An increased frequency of tumor-infiltrating T-lymphocytes especially Tregs can associate with a poorer prognosis but a potential role for these cells in the pathogenesis and progression of colorectal cancer may be implicated by more comprehensive studies.

Hereditary aspects in colorectal cancer

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Introduction: Colorectal cancer is one of the major malignancies worldwide. The genetic interaction responsible for increasing incidence is demonstrated.

Aim of study: Our study identified the parameters of age and family aggregation of cancer that could allow it to be classified as hereditary colorectal cancer.

Material and methods: Our study included 215 patients with colorectal cancer examined and endoscopic diagnosed from January 2006 to January 2010. Statistically the majority were male patients (60.46% men comparative with 39.54% women). The medium age was 55 ± 7 years. The genetical, clinical, biochemical and endoscopical evaluation has been complete.

Results and discussion: Family aggregation in our cases of colorectal cancer was in a proportion of 16.27% (35 patients). 4 patients (1.86%) presented hereditary polyposis colorectal cancer. 14 patients (6.51% of the cases) met all the "Amsterdam criteria" and could allow their classification as hereditary non-polyposis cancer (Lynch syndromes). Beside the 12 cases family history of colorectal cancer, cases with family history of gastric neoplasm (2), breast neoplasm (2) and esophageal neoplasm (1) were also identified. Two cases belonged to a family in which all the three brothers developed colorectal cancer before the age of 30. A very uncommon case was represented by a family of a 39 year old patient, in which 6 of the 10 members belonging to successive generations had neoplasias.

Conclusions: Family aggregation in colorectal cancer is high (16.27%). The screening of colorectal cancer included and genetic screening of people with high risk.

Traditional diet, heavy smoking and alcohol abuse as risk factors for developing colorectal cancer

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Introduction: Diet and lifestyle factors have a significant influence on the risk of developing colon cancer. The aim of this study was to establish the relationship between environmental factors and colon cancer incidence in 118 patients with colorectal cancer (CRC) hospitalized in The IVth Medical Clinic of University of Medicine and Pharmacy, Timisoara.

Methods: The sex repartition of the patients was 56.60% men and 44.4% women. All the patients were complete investigated: clinical exam, laboratory tests, colonoscopy, and histopathological exams.

Results: 68% of them were heavy smokers (> 20 cigarettes/day). 23% of them had a history of drinking alcohol > 300 ml/day. Patients from rural area were 62% and from urban area 38%. The diet of the patients with CRC comprised: 52% smoked meat, 48% animal fats. Family history of CRC had 27% of them. The presence of colonic polyps was higher in heavy smokers comparative with non-smokers (48% vs. 16%). 43% of them had a sedentary life.

Discussion/Conclusion: Traditional diet with smoked meat and animal fats associated with heavy smoking, alcohol abuse and a sedentary life are important risk factors for development of CRC. Colonoscopy is the first-line colorectal-cancer screening option in patients with suspicion of having CRC.

Prevalence of type 2 diabetes and other risk factors in patients with colorectal cancer

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Introduction: People with type 2 diabetes have an increased risk of developing colorectal cancer. Both type 2 diabetes and colorectal cancer share some of the same risk factors (like excess weight). The aim of this study was to determine the risk factors for patients with colorectal cancer and the prevalence of type 2 diabetes mellitus in these patients.

Methods: The study was designed in The IVth Medical Clinic of University of Medicine and Pharmacy Victor Babes, Timisoara in one year period: January 2008 to December 2009. The patients were complete investigated and we measured anthropometric parameters for every patient.

Results: The age of the patients was 56.02 ± 20.15 . 17% of the patients had type 2 diabetes mellitus. 39.58% of the patients with type 2 diabetes mellitus had colorectal cancer. The location of the colorectal cancer was: 39.58% on the rectum, 31.25% on the left bowel, 14.58% on the transverse bowel and 14.58% patients on the right bowel. 48% of the patients with associated type 2 diabetes mellitus and colon cancer were overweight with BMI between 25–30 kg/m² and 16% of them presented obesity (BMI \geq 30 kg/m²). 52% of the patients had a sedentary life.

Discussion/Conclusion: Patients with colorectal cancer and type 2 diabetes had a greater risk for a worse outcome. Chronic insulin therapy significantly increases the risk of developing colorectal cancer among type 2 diabetes mellitus patients.

Colonic expression and systemic concentration of vascular endothelial grow factor (VEGF) in ulcerative colitis

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Introduction: Inflammatory bowel disease (IBD) has environmental and genetic background. Angiogenesis plays important role in IBD, however data concerning expression and profile of vascular endothelial grow factor (VEGF) in patients with ulcerative colitis (UC) are contradictory. The German investigators (T. Griga et al. *Scand J Gastroenterol*, 1998; 33: 504–508, and T. Griga et al. *Hepatogastroenterology*, 2002; 49: 116–123) demonstrated VEGF overexpression in UC – inflamed intestine and increased VEGF serum concentration in UC patients, whereas the Greek investigators (A. Giatromanolaki et al. *J Clin Pathol*, 2003; 56: 209–213, and A. Kapsoritakis et al. *Int J Colorectal Dis*, 2003; 18: 418–422) presented only weak intestinal VEGF expression and similar VEGF concentration in circulation in active UC patients and control subjects.

Methods: We investigate the profile of VEGF in colonic tissue and its level in plasma and serum in patients with UC. The localization of VEGF protein in intestinal tissue was estimated by immunohistochemistry, and the level of protein was measured by optical density analysis. VEGF concentration in serum and plasma in UC patients was determined by ELISA.

Results: The specific staining reaction for VEGF protein was significantly ($p < 0.001$) higher in active UC intestine compared with controls. Serum level of VEGF was significantly higher ($p < 0.01$) in active UC patients ($114.4 \text{ pg/ml} \pm 69.6$), compared with inactive UC patients ($44.3 \text{ pg/ml} \pm 27.4$), and when compared with controls ($39.7 \text{ pg/ml} \pm 31.2$). Similarly the plasma VEGF level was found to be significantly higher ($p < 0.05$) in active UC patients ($45.3 \text{ pg/ml} \pm 3.5$) compared with controls ($42.6 \text{ pg/ml} \pm 1.8$).

Discussion/Conclusion: The profile of VEGF in UC obtained in our study is similar to the findings of the German investigators, and mostly different from the results of the Greek researchers. It may suggest that different environmental factors and/or genetic backgrounds in northern Europe and the Mediterranean area may influence VEGF expression in UC – intestine.

Surgical treatment in patients with inflammatory bowel diseases – A retrospective study

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Introduction: Data about surgical treatment in inflammatory bowel diseases (IBD) in Romania are scarce.

Material and methods: 25 patients hospitalised in Railway Hospital Cluj-Napoca with IBD were included in a retrospective (2003–2009) study. All suffered one or more surgical interventions for the treatment of IBD. We followed the indications, type of surgery, postoperative complications and the number of interventions per patient.

Results: 11 (44%) were diagnosed with Crohn's disease (CD), 14 (56%) with ulcerative colitis (UC). CD patients: 4 women (36.3%), 7 men (63.6%), median age (MA) for the first surgical intervention was 37.5 years, MA at the diagnosis of CD was 34.85 years. BC colonic: 4/11 (36.3%), ileal: 2/11 (18.2%), ileocolic: 2/11 (18.2%), gastric: 1/11 (9%). 12 surgical interventions were performed for: stenoses (6/12, 50%) (3 on the colon, 3 on the ileon), fistula (4/12, 33.3%) (3 ano-rectal, 1 ileocolic), colonic carcinoma (1/12, 8.3%), suspicion of neoplasm/miss diagnosis (1/12, 8.3%). Immediate complications: anastomotic fistula (3/9, 33.3%) treated surgically. In total, 15 surgical interventions were performed in the 11 patients with CD (1.35/patient). UC patients: 6 women (42.8%), 8 men (57.2%), MA of the first surgical intervention was 37.16 years, MA at the diagnosis of UC was 33.16 years. Indications for surgery: corticosteroid-resistant UC (7/14, 50%), fulminant pancolitis (5/14, 35.7%), carcinoma suspected (1/14, 7.14% with high grade dysplasia on histology exam), suspicion of colonic polyposis/miss diagnosis (1/14, 7.1%). Types of interventions: total colectomy with ileo-recto-anastomosis (11/14, 78.6%), proctocolectomy with ileo-anal anastomosis with pouch (2/14, 14.3%), partial colectomy with right colostoma, sigma closed, in place (1/14, 7.14%). Immediate complications: anastomotic fistula (5/14, 35.7%), anastomotic fistula complicated with peritonitis (1/14) abdominal wall abscess (1/14). Late complications: perianal fistula (1/14), ileo-cutaneous fistula (1/14), colocutaneous fistula (1/14). In total, 25 surgical interventions were performed in 14 patients with UC (1.78/patient).

Conclusions: Surgical treatment in IBD is not standardised in Romania. Postoperative complications are frequent and necessitate a good cooperation gastroenterologist/surgeon.

Biological regulating substance at ulcerative colitis

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The study of clinical and pathogenic importance biological regulating polypeptides (growth's factors) at ulcerative colitis.

Introduction: Inflammatory bowel disease (IBD), which includes ulcerative colitis (UC) and Crohn's disease (DC) represent a serious medical and social problem. In recent years, preference is given to the hypothesis of immunogenetic and growth factors that stimulate the differentiation of various cells and are the main carriers of the mitotic signal.

Methods: A total of 146 patients with UC (54 men and 92 women) mean age (35.7 ± 12.8 years). All patients were randomized into 3 groups: I group – 64 patients with left-sided localization and moderate UC; II and group III – 48 and 34 patients with a total localization of UC, moderate and severe with high disease activity, respectively. The control group – 25 healthy volunteers, mean age 21.7 ± 3.52 years. Activity of disease was assessed by periodical clinical, endoscopic and histological examinations. The content of the growth's factors (epidermal growth factor and insulin like growth factor) were measured in homogenates colon biopsies with the help immunofluorescent analysis.

Results: An inverse relationship between the production of epidermal growth factor (EGF) and insulin like growth factor (IGF), and the degree of activity of UC. In all groups of patients reported reduction in EGF. In all groups of patients is registered decrease level EGF. In the first and second groups of reducing the concentration of EGF was 69.1 ± 13.6 pg/g and 35.31 ± 10.3 pg/g, which is in 1.3 and 2.6 times was lower than in the group of healthy volunteers. In the third group of patients registered with the lowest possible level of EGF in the colon SB – 26.2 ± 7.71 pg/g, which is 3.6 times lower than the control values ($p < 0.05$). The maximum decrease in production of IGF detected in patients with second and third groups: 49.1 ± 12.52 pg/g and 34.13 ± 9.47 pg/g, respectively, in 3.3 and 3.9 times lower than the reference values of healthy volunteers ($p < 0.05$). A high correlation between rectal bleeding, index activity UC Mayo and concentration of EGF in the mucous membrane colon ($r = 0.58$, $p = 0.04$), ($r = 0.64$, $p = 0.05$) and ($r = 0.77$, $p = 0.01$), respectively.

Discussion/Conclusion: We have assessed the highest possible changes in production of biological regulating substance (growth's factors) in colon's mucous, which are in direct dependence upon the duration and degree of ulcerative colitis, which allowed us to use them as an integral index of disease activity.

Effectiveness of Salofalk[®] and Budenofalk[®] in the treatment of severe forms of ulcerative colitis and preparing the defunctionalized portions for reconstructive operations

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Introduction: Expansion of indications for elective colectomy and the possible preservation of the corresponding portion of the rectum or the ascending colon, which is the most important element of the surgical rehabilitation.

Methods: Within 1980–2009, 442 patients with various clinical forms of disease, level of activeness and incidence of nonspecific ulcerative colitis got treatment in our surgical clinic: **retrospective group** (1980–1990, **sulphasalazine, systemic corticosteroids**) – 155 patients, and **experimental group** (1991–2010, **Salofalk[®], topical corticosteroids – Budenofalk[®]**) – 287 patients. Scheme of patient examination: clinical and special proctologic investigation; colonoscopy with serial biopsy; irigography; determination of basal mucous membrane infiltration using the histomorphometric method by Avtandilov G.; balloonographic sphincterometry; coprologic and immunologic investigations.

Results: Surgical intervention was carried for 53 (34.2%) patients of the *retrospective* and 62 (21.6%) patients of the *experimental* groups. Surgical activity was 1.6 times higher in the *retrospective group*. Urgent surgery was performed on the overwhelming majority of patients, while in the *experimental group* planned colectomy was performed twice more often.

Discussion/Conclusion: 1. **Salofalk[®]** and **Budenofalk[®]** are the drugs of choice in the treatment of serious widespread forms of nonspecific ulcerative colitis, lowering the risk of complications requiring colectomy by 1.5–2 times, as compared to the *sulfasalazine* and the *prednisolone*. 2. The **Salofalk[®]** in rectal suppositories and enema is an effective method of preparing the defunctionalized rectosigmoid portion (after subtotal colectomy) for the reconstructive operation. 3. The **Salofalk[®]** in rectal suppositories and enema, and **Budenofalk[®]** in capsules are reliable pharmaceutical solutions in suppressing the recurrent inflammations in the preserved rectum and the brought-down ascending colon after the reconstructive surgical operations.

Comparison of primarily diet-modifiable intestinal factors, Cx-43 and E-cadherin with P53 and TGF-beta1 – A diversity of correlations among their diet-independent, autonomous expressions in colorectal cancer

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Introduction: Primarily, a diet (particularly dietary lipids and vitamins) can reversibly modify intestinal expressions of a few factors like Cx-43, E-cadherin, P53 and TGF-beta1 with a special impact on immunity and mutagenesis. Anyway, malignant phenotype constitutes a diet-resistant signal streaming with engagement of these molecules which are generated in autonomous ways in colorectal cancer. We aimed to compare adhesion proteins: Cx-43 and E-cadherin with P53 and TGF-beta1 in colorectal adenocarcinomas.

Methods: Cx-43 and E-cadherin with P53 and TGF-beta1 were detected with immunohistochemistry in the study of 106 colorectal adenocarcinomas.

Results: There was aberrant cytoplasmic expression instead of membranous one of Cx-43 and E-cadherin reflecting constitutive destruction of intercellular ties while P53 showed nuclear expression and TGF-beta1 accumulated in the cytoplasm. P53 didn't correlate with Cx-43 ($r = 0.083$, $p = 0.397$) but correlated with E-cadherin ($r = 0.199$, $p = 0.041$). E-cadherin associated with TGF-beta1 reaching almost statistical significance ($r = 0.188$, $p = 0.054$), while TGF-beta1 correlated with Cx-43 ($r = 0.359$, $p = 0.001$).

Discussion/Conclusion: There can be predominance of production over protein utilization because of overexpression of Cx-43, E-cadherin, P53 and TGF-beta1 due to eventual underlying mutations causing intracellular storage of mentioned markers in colorectal cancers. The consequent and constant impairment of cancer intercellular communication seems to engage aberrantly abundant or abnormally located and mutually associated expressions of proteins: Cx-43, E-cadherin, P53 and TGF-beta1 in cancer cells. This particular pattern of co-expression appears to be stable and constitutive for malignant phenotype of colorectal cancers in opposition to transiently activated cells with reversible immunoprofile in benign inflammatory process.

Liver-associated macrophages via TNF-alpha might induce non-alcoholic fatty liver disease in type II diabetes mellitus patients

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Introduction: Increased TNF-alpha mRNA in liver of patients with non-alcoholic fatty liver disease (NAFLD) was described mainly in type II diabetes mellitus. Data from animal and clinical studies indicate that TNF-alpha mediates not only the early stages of fatty liver disease but also the transition to more advanced stages of liver damage. The aim of the present study was to evaluate liver TNF-alpha expression in patients with type II diabetes mellitus and to compare its intensity to the numbers of CD68-positive cells part of which are Kupffer cells, the main TNF-alpha producers in the liver.

Methods: Liver samples from 13 autopsied patients with type II diabetes mellitus and clinical features of liver disease and 6 surgical biopsies without signs of liver pathology who served as controls, were investigated with antibodies against CD68 and TNF-alpha.

Results: Livers of diabetic patients showed signs of mild portal inflammation, mild to intense fibrosis and presence of septa that emerged from portal tracts to zone 1. The lobules contained micronodular steatosis. We diagnosed this histology as non-specific reactive hepatitis or as non-alcoholic fatty liver disease. The more intense expression of TNF-alpha in portal tracts correlated with the presence of fibrosis in portal tracts ($\chi^2 = 12.4$, $p = 0.002$) and of septa in zone 1 ($\chi^2 = 12.4$, $p = 0.002$). An association was found between the high number of CD68 positive cells in liver sinusoids and the more expressed TNF-alpha reaction there ($p < 0.001$). As compared to controls CD68 positive cells were increased in numbers in portal tracts (28.13 ± 24.79 vs. 0.97 ± 0.41 , $p = 0.002$) and lobules (51.59 ± 28.33 vs. 1.28 ± 1.95 , $p = 0.002$) in the liver of all patients with NAFLD.

Discussion/Conclusion: In conclusion we may state that activation of liver associated macrophages (CD68 positive Kupffer cells and sinusoidal monocytes) might induce the appearance of NAFLD via TNF-alpha.

Vitamin D receptor (NR 1|1) polymorphisms as a genetic basis for vitamin D-mediated effects on the therapy response in chronic hepatitis C patients

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Introduction: Chronic hepatitis C virus (HCV) infection represents a leading cause of end stage liver disease. Non-parenchymal hepatic cells as mediators of inflammation and fibrogenesis such as Kupffer cells and stellate cells do express VDR protein. Given the established role of vitamin D as an immunomodulator and recent data on HCV therapy response, it is straightforward to investigate the effects of common vitamin D receptor *VDR (NR 1|1)* polymorphisms on hepatic inflammation and therapy response.

Methods: Overall, 166 patients with available blood samples and liver biopsies were included for TaqMan *VDR* genotyping (Cdx2 rs11568820, bat-haplotype consisting of Bsm rs1544410, Apa rs 7975232 and Taq rs 731236). Statistical associations with Metavir A-score and sustained virological response (SVR) to PEG-interferon/ribavirin standard therapy were calculated.

Results: The Apal (CC) and Taql (TT) genotypes showed a significant correlation with HCV-therapy failure (non-SVR vs. SVR; Apal p = 0.037; CC vs. CA/AA p = 0.012; OR = 2.66; Taql p = 0.018; CC vs. CA/AA p = 0.002; OR = 6.05). Likewise, the most frequent bAt-haplotype (Bsm CC_Apa CC_Taq TT) was associated with non-SVR vs. SVR (p = 0.005 vs. any particular other haplotype; p = 0.009 vs. all other haplotypes combined; OR = 2.66). Of note, 62.2% of bAt-haplotype patients are non-responders. In addition, also Cdx2 TT is also associated with non-SVR (p = 0.016 for TT vs. CT/CC) but the small number of TT-nonresponders (n = 5) limits definite conclusions. Logistic regression analysis between the observed haplotypes confirmed Apal CC and Taql TT as two significant (for Apal CC p = 0.043; for Taql TT 0.019) and frequently coexisting polymorphisms with respect to all occurring haplotype combinations. No significant association was observed for any *VDR* genotype or haplotype to Metavir inflammatory activity.

Discussion/Conclusion: *VDR* polymorphisms are significantly associated with the therapeutic response to interferon/ribavirin in chronic HCV-patients. Our data characterize a genetic basis of vitamin D-signalling as another important component of beneficial vitamin D effects.

Non-alcoholic fatty liver disease (NAFLD): What we need?

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Introduction: Over millions of years, the extremes of the environment, short periods of abundance interspersed with long periods of food shortages have led the development of a metabolic apparatus suitable for fat storage, disposal and insulin resistance as a means of preserving the protein stocks. The actual super-abundance and inactivity broke this balance with the growth of obesity over world. Part of the picture, over 30% of adults and 20% of children have fatty liver disease. Our objective was to evaluate the improvement of NAFLD with exercise and diet rich in fiber.

Methods: Subjects with BMI > 25.0 underwent physical examination, biochemical tests (AST/ALT ratio, ALP, GGT, glucose, cholesterol, HDL, triglycerides) and CT (without contrast) to calculating the liver/spleen density ratio (LSR) (Hounsfield units). Those with NAFLD have targeted dietary fiber (30 g/d) and exercise (3 times a week for 60 minutes) along 12 weeks. At the end of the period we repeated the measures.

Results: We evaluated 67 subjects, 77.6% females and 22.4% males with 55.9 ± 10.9 years old and BMI = 31.2 ± 4.2 kg/m². The prevalence of NAFLD, as measured by CT with LSR < 1.0, was 35.8%. In these subjects we found AST/ALT ratio < 1.0, higher levels of GGT, triglycerides, fasting glucose and lower levels of HDL when compared with the non-NAFLD subjects ($p \leq 0.05$). To date, 11 of NAFLD subjects completed 12 weeks of exercise and diet with a significant reduction ($p = 0.002$) of liver steatosis (LSR ≥ 1.0) in 91% of cases and reduction of GGT, triglycerides and raising HDL in the majority.

Discussion/Conclusion: We conclude that with few exceptions, the changes in lifestyle, including physical activity and healthy diet are sufficient for control of NAFLD.

Comparative analysis of steatohepatitis in non-alcoholic fatty liver disease and chronic hepatitis C

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Introduction: Non-alcoholic fatty liver disease (NAFLD) and infection with hepatitis C virus (HCV) are frequent causes of chronic liver diseases. NAFLD is strongly associated with metabolic syndrome (MS), but chronic hepatitis C may also have some features of MS, either viral induced, either with metabolic background.

Aim: To assess the impact of clinical, demographical and laboratory findings on the presence of steatohepatitis both in NAFLD and in chronic hepatitis C.

Methods: We included in the study 196 subjects with NAFLD (98) and HCV infection (98), genotype 1. Extensive clinical, demographical and histological data were available. We assessed the presence of steatohepatitis component using Kleiner score. According to the value of NASH Activity Score resulted from histological data, we divided the group into three categories: NASH, borderline and No NASH and we compared the study groups using univariate and multivariate analysis.

Results: Irrespective of the studied group, all patients had the features of MS, but NAFLD patients were more obese (higher BMI and waist circumference [$p = 0.001$]), diabetic ($p = 0.001$), hypertensive ($p = 0.001$) and hyperlipidaemic ($p = 0.0001$). The insulin resistance evaluated by glycaemia, insulinaemia and HOMA-IR was found in both groups, but was more expressed in NAFLD ($p = 0.001, 0.03, 0.01$). By multivariate analysis we could not find independent predictive factors for steatohepatitis in one of the diseases.

Discussion/Conclusion: These results suggest that steatohepatitic component in both diseases belongs to metabolic syndrome and it is not induced by the virus.

Nutritional, medication and exercise influences on non-alcoholic fatty liver disease

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Introduction: Non-alcoholic fatty liver disease (NAFLD) falls into a spectrum of liver diseases characterized by macrovesicular fatty degeneration in the absence of significant alcohol consumption. NAFLD is caused by multiple factors of which most view in practice are: nutritional causes, drugs, metabolic disease, insulin resistance or exposure to toxins.

Methods: We conducted a prospective observational investigation on 125 patients with NAFLD trying to identify any features of this patients in our geographical area (frequency and type of risk factors, clinical aspects, associated diseases, biochemical characteristics). The data were analyzed versus a control group. Patients completed a questionnaire regarding lifestyle, age, gender, environment of origin, food behaviour, degree of physical activity, smoking, medication.

Results: Analyzing patients depending on the environment indicates that many come from urban areas (69%) and women are highly represented. Age group best represented was 50–59 years, following 40–49 and 70–79 years. Distribution according to lifestyle reveal a significant percentage of patients that recognize a sedentary lifestyle (79.2%), low or medium fruit and vegetables intake, nutrition with high carbohydrates/high lipids load.

Discussion /Conclusion: Results confirm data from literature according to which non-alcoholic fatty liver is a disease more common in the adult population than originally thought, being accompanied by multiple comorbidities. We confirm the high prevalence of obesity, metabolic syndrome and cardiovascular pathology in a sedentary population with an unhealthy life style.

It is very justified an action of aggressive prevention, correction and treatment of obesity and associated factors addressed towards all sections of the population by promoting physical exercise (the cheapest and effective treatment for NAFLD) and a style of healthy eating, based on increased consumption of fibers, fruits and vegetables in order to prevent cardio-metabolic morbidities. Information and involvement of health professionals at all levels is not sustained nor sufficient and the addressability or adherence/compliance of patients to change their lifestyle is far from an acceptable threshold.

Correlation between US severity of steatosis and insulin resistance indices in adult patients affected by non-alcoholic fatty liver disease

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Introduction: Non-alcoholic fatty liver disease (NAFLD) is a common finding in the general Italian population ranging from 20 to 30% of adult. The diagnosis of NAFLD is usually made by liver US examination and confirmed, only in some cases, by liver biopsy.

Aim of this study was to assess the correlation between severity of ultrasonographic hepatic steatosis and degree of obesity, insulin resistance and serum biochemical abnormalities.

Methods: We perform a cross sectional study on a sample of 50 adult patients undergone US scan at our US Unit. All patients were enrolled after finding of steatosis at US scan of the liver, exclusion criteria were: infection by HBV, HCV, HIV, Alcohol intake upper than 30 g/day, patent NIDDM, diagnosis of autoimmune hepatitis, CBP, CSP, liver cirrhosis, HCC and other liver malignancies. All subjects underwent physical examination, anthropometric and real-time ultrasonographic (US) examination of the liver. Fasting blood samples were collected for the measurement of liver function, hepatitis status, levels of serum glucose and insulin and lipid profile. Degree of fatty infiltration of the liver was graded according to ultrasonic appearance of liver echotexture, liver-diaphragm differentiation in echo amplitude, hepatic echo penetration and clarity of hepatic blood vessels.

Results: Fifty patients were included in the study, 21 males and 29 females, median age was 54.6 years (range 23–70). The severity of fatty liver was positively related to anthropometric measurements including BMI, waist circumference; insulin resistance markers [QUICKI and homeostasis model assessment (HOMA)], and hypertriglyceridemia. Combination of hepatic steatosis with raised ALT (presumptive NASH) was found in 21 subjects (42%). This group of patients had significantly higher waist circumference compared to those with isolated hepatic steatosis. Males with presumed NASH were also found to have significantly higher insulin resistance.

Discussion/Conclusion: The prevalence of simple steatosis and presumed NASH was 58 and 42%, respectively. The severity of US steatosis was positively correlated with BMI, raised ALT, insulin resistance and hypertriglyceridemia.

Ultrasonography being non-invasive and readily available could be used for the monitoring of hepatic steatosis and insulin resistance.

Cardio-pulmonary dysfunction and endothelin levels in cirrhosis

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Introduction: Patients with cirrhosis and cardio-pulmonary complications have increased risk for complications and mortality, especially after liver transplantation. The evolution of porto-pulmonary hypertension in cirrhosis is very well correlated with some parameters like interleukins, endothelins and NT pro-BNP. The present study was aimed to investigate the plasma levels of endothelin in cirrhosis and to correlate them with the severity of the liver disease.

Methods: We compared 65 healthy subjects with 65 cirrhotic patients regarding clinical presentation, biological parameters, abdominal and cardiovascular ultrasonography, electrocardiography and plasmatic endothelin levels.

Results: According to the severity of the liver disease, 13.8% of patients was included in Child A, 49.2% in Child B and 36.9% in Child C score. The highest endothelin levels were found in patients with cirrhosis and ascites (38.66 ± 65.14 fmol/ml) comparatively with compensated cirrhosis (2.315 ± 1.99 fmol/ml) or controls (0.26 ± 0.18 fmol/ml). Determinants of endothelin were examined using multivariate regression analysis and the best predictors were transaminase levels ($p = 0.02$) and increased pulmonary pressure ($p = 0.003$). Endothelin levels correlates with all ecographically assessed parameters of portal hypertension: portal vein diameter ($p = 0.011$, $r = 0.32$), splenic vein diameter ($p = 0.01$, $r = 0.33$), portal vein flow velocity ($p < 0.01$, $r = 0.71$).

Discussion/Conclusion: Circulating levels of endothelin are significantly elevated in liver cirrhosis and represent the most powerful expression of porto-pulmonary hypertension.

Combined therapy in association with lifestyle changes in the treatment of patients with non-alcoholic steatohepatitis

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Introduction: The aim was to evaluate and compare the effectiveness of UDCA monotherapy, simvastatinum and combination of UDCA and vitamin E, in association with therapeutic lifestyle changes, for the treatment of NASH in obese patients.

Methods: We studied 53 patients with NASH and obesity. We excluded patients with viral or autoimmune hepatitis, diabetes mellitus or drug abuse. The diagnosis was based on the correlation of histological and clinical findings. Liver biopsy was performed before and after therapy.

A group composed of 18 normolipidemic cases, treated with UDCA 13–15 mg/kg/day, B group consist of 15 hyperlipidemic cases which received simvastatinum 20 mg/day and C group (20 patients) with UDCA and vitamin E (400 IU twice a day) therapy. We evaluated liver function tests, serum lipids, BMI and Brunt's score at baseline, after 6 and 12 months. Also, we asses and monitor the main therapeutic lifestyle changes: diet, exercise, weight loss and stop smoking cigarettes.

Results: A number of 39 patients had elevated serum aminotransferase level, but 14 had normal values. In B group, lipide profile was: 7 cases with hypercholesterolemia, 4 cases with hypertriglyceridemia and 4 with both.

In A group, mean value of serum ALT-level was decreased from 88.3 ± 21.7 U/l at baseline, to 52.12 ± 17.5 U/l at 6 months. In B group, serum ALT was reduced (in mean with 19.3 ± 7.2 U/l) after 6 months and cholesterolemia was significantly improvement in 8 cases (72.7%). In 2 cases we increased simvastatinum dose at 40 mg/day. In C group mean ALT and AST levels was more decreased: in mean with 49.3 ± 5.2 U/l. After one year, aminotransferase levels reach normal range only in C group. Comparatively, in A and B groups the rates of ALT was lower (89.7% and 73.33%). Histopathologic exam indicate improvement the steatosis grade: 83.3% in A group, 73.3% in B group and 90.0% in C group. We could not establish a correlation between the values of serum aminotransferases and others parameters, but multivariate analysis showed that the BMI > 28 kg/m² and elevation of serum ALT were associated with steatosis grade. Patients which associated combined therapy with low caloric diet had a good and rapid response.

Discussion/Conclusion: Combination of UDCA and vitamin E significantly improves aminotransferase levels and steatosis grade. The combined therapy and low caloric diet still remains first line therapy in patients with NASH and obesity.

Prevalence of immature dendritic cells and of CD4⁺ T-lymphocytes in fatty liver disease in diabetes mellitus type II

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Introduction: Non-alcoholic fatty liver disease (NAFLD) is commonly associated with type II diabetes mellitus. NAFLD is presented by mild mononuclear portal inflammation, fibrosis and steatosis. The aim of our study was to assess the presence of some immune cells and TGF-beta 1 in sinusoids and portal tracts in livers of patients with type II diabetes mellitus.

Methods: Liver samples were obtained from 13 autopsied patients with type II diabetes mellitus and clinical features of liver disease and 6 surgical biopsies without signs of liver pathology who served as controls. Liver histology was assessed on preparations stained by haematoxylin/eosin and Van Gieson. Immunohistochemistry was done with antibodies against CD1a, CD83, CD4, CD8, CD56 and TGF-beta 1.

Results: As compared to controls NAFLD livers showed statistically increased numbers of CD4⁺ (3.27 ± 3.43 vs. 0.86 ± 0.59 , $p = 0.03$) and CD8-positive cells (5.85 ± 5.06 vs. 0.8 ± 0.37 , $p = 0.006$) in sinusoids. CD1a- and CD83-positive cells prevailed in sinusoids of NAFLD livers in comparison to controls (5.57 ± 3.55 vs. 1.52 ± 0.96 , $p = 0.044$ for CD1a; 4.57 ± 3.02 vs. 1.27 ± 1.95 , $p = 0.02$ for CD83) and CD83 in portal tracts (4.54 ± 6.47 vs. 0.97 ± 0.41 , $p = 0.035$). The increased TGF-beta 1 expression in liver lobules was correlated with the higher number of CD1a-positive cells in liver sinusoids ($p = 0.02$). The increased TGF-beta 1 expression in portal tracts and lobules was correlated to increased CD4-positive cells numbers there ($p < 0.05$).

Discussion/Conclusion: Probably TGF-beta 1 released by hepatic stellate cells suppresses dendritic cells maturation in liver sinusoids. It might be supposed that TGF-beta 1 is chemoattractant for CD4-positive lymphocytes in the lobule, where CD4-positive lymphocytes might exert a regulatory function.

Lead nitrate induces toxic liver damage and stem cell activation in rat liver

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Lead nitrate (LN) is known as the widespread industrial toxin and a direct mitogen for hepatocytes' proliferation. However, we previously demonstrated that a single injection of LN induced morphological changes in the liver and stimulated reparative regeneration manifested in the proliferation epithelial and sinusoidal liver cells and hepatic stellate cells' activation. But mechanisms of the damaging effect of LN on the liver and possibility of stem cell activation are not known. So, the aim our study was to investigate biochemical features of the liver damage induced by LN and expression of the Stem Cell Factor Receptor C-kit – one of the stem cells' marker – after this damage.

Rat's liver specimens after single intravenous injection of LN were investigated biochemically and immunohistochemically. We found that main mechanism of liver's damage is lipid peroxidation. The paraffin liver sections were stained with antibodies to C-kit. After 2 days after injection of LN and later we observed C-kit⁺ hepatocytes and sinusoidal cells. Double immunohistochemical staining shown the most of these sinusoidal cells expressed desmin also (desmin is a marker of the hepatic stellate cells). Thus, during liver regeneration after its damage by LN the activation of C-kit⁺ stem cells occurs, and hepatocytes and hepatic stellate cells demonstrate stem cell's phenotype. We can suppose the development of the C-kit⁺ hepatocytes from C-kit⁺ hepatic stellate cells.

Ultrastructure of the liver progenitor/oval cells in children with non-alcoholic steatohepatitis. The first report in pediatric patients

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Introduction: The role of the liver progenitor/oval cells (syn. hepatic stem cells) in the morphogenesis and development of non-alcoholic steatohepatitis (NASH) both in patients and experimental animals has gained an increasing interest reflected in literature reports. The aim of the study was to evaluate the ultrastructure of the population of liver progenitor/oval cells in the biopsy material from children with previously clinicopathologically diagnosed NASH. This is the first literature report on the subject in children.

Methods: Electron-microscopic examinations were conducted on fresh tissue samples collected from 10 children with NASH (aged 2–14 years), which were fixed with solution of 2% paraformaldehyde and 2.5% glutaraldehyde in 0.1 M cacodylate buffer.

Results: Our ultrastructural examinations of the liver progenitor/oval cells in children with NASH indicate a significant increase in this population of liver cells, especially their two types, hepatic progenitor cells (HPCs) and intermediate hepatocyte-like cells (IHCs), with intermediate bile-like cells being the least frequent. They were found to occur single or in clusters of two, seldom of three, and frequently in the areas of advanced liver fibrosis or close to them. Many times, these cells were accompanied by hepatocytes showing of varied degree of death, to total cell disintegration. Interesting was the presence of activated nonparenchymal liver cells, i.e. Kupffer cells/macrophages and hepatic stellate cells, frequently found to adhere to the hepatic oval cells.

Discussion/Conclusion: The current study suggests a marked involvement of the population of liver progenitor/oval cells, mainly HPCs and IHCs, in the development of NASH in children, especially in fibrosis progression. It is very likely that activation of hepatic stem cells persisting in the course of NASH since childhood and coexisting with advanced fibrosis may increase the risk for hepatocellular carcinoma in adulthood.

The prevalence of non-alcoholic liver disease (NAFLD) amongst patients with the metabolic syndrome

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Introduction: The prevalence of non-alcoholic fatty liver disease (NAFLD) in Romania is unknown. The World Health Organisation (WHO) criteria for diagnosing the metabolic syndrome include the presence of insuline resistance, dyslipidaemia, hypertension and obesity.

Aim and methods: A prospective study was carried out, including 696 patients with persistently elevated liver tests and metabolic syndrome. We standardized the laboratory tests sequence, including complete hepatic functional exploration, abdominal ultrasound and liver biopsy. Features of the metabolic syndrome were assessed. Statistical analysis was performed using SPSS and significance determined by independent sample t-test.

Results: 82 patients had alcoholic liver disease (all with alcohol disease intake) and 114 patients had non-alcoholic liver disease (NAFLD). In alcoholic liver disease and metabolic syndrome group mean age was 49 years and body mass index 31 and in NAFLD and metabolic syndrome group mean age was 56 years and body mass index 33. All 114 patients with NAFLD were offered a liver biopsy, and this was performed in 101. The biopsies were normal in 6 patients, showed simple steatosis in 46 patients non-alcoholic steatohepatitis (NASH) in 41 patients and cirrhosis in 8. Patients with cirrhosis were older than those with NASH and simple steatosis and have more features of the metabolic syndrome.

Conclusions: The prevalence of alcoholic liver disease with metabolic syndrome is frequently in Romania. With an increasingly obese and ageing population, the prevalence of chronic liver disease is predicted to rise.

Non-invasive markers as predictor factors for fibrosis in non-alcoholic fatty liver disease

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Non-alcoholic fatty liver disease (NAFLD) is a frequent syndrome encompassing fatty liver alone and steato-hepatitis (NASH). The gold standard in diagnose NAFLD is liver biopsy.

The **aim** of our study was to find the concordance between liver biopsy and non-invasive methods.

Methods: We included 54 patients with NAFLD (31 females and 23 males) with mean age 54.06 years. We excluded the patients with other conditions known to be associated with hepatic steatosis (including alcohol consumption).

In all patients we measured: BMI, waist circumference, aminotransferases (ALT, AST), triglycerides, gamma-glutamyltranspeptidase (γ -GT), alkaline phosphatase (AP) and serum adipokines (leptin, adiponectin). We calculated the BAAT score as a sum of categorical variables: BMI, age, levels of ALT and serum triglycerides, ranging from 0 to 4. A score of 0 or 1 would suggest patients without septal fibrosis. Steatosis was evaluated by US and we used a semiquantitative scale of 1 (mild) to 3 (severe). All patients benefit from a liver biopsy and we used Matteoni's classification for the histological samples.

Results: BAAT score correlated positively with histological features ($p = 0.000$) and leptin level ($p = 0.002$) and negatively with adiponectin ($p = 0.000$). We didn't find any correlation with US classification ($p = 0.955$). BMI correlated positively with histological classification ($p = 0.001$), leptin ($p = 0.000$), US ($p = 0.02$) and negatively with adiponectin ($p = 0.013$), but no correlation between BMI and aminotransferases. Waist circumference didn't correlate with histological features and adiponectin level but correlated with leptin ($p = 0.000$). Aminotransferases and US description didn't correlated with histological classification. Adiponectin correlated negatively with histological features ($p = 0.000$) but we found no relationship between leptin level and histological classification.

Conclusions: In our study the association between anthropometric measures, US steatosis biochemical markers could not replace biopsy liver but some association like BMI, high levels of triglycerides and BAAT score, low level of adiponectin represent non-invasive markers for the selection of patients who require liver biopsy.

Is there a correlation between metabolic syndrome and liver lesions?

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Introduction: Non-alcoholic fatty liver disease is one of the most common liver diseases. Its prevalence among patients with metabolic risk factors (obesity, type 2 diabetes, hypertension, lipid disorders) without previously recognized liver disease is not completely known.

Aim of our study was to determine the prevalence of liver disease (elevated alanin aminotransferase (ALT), gamma glutamyl transpeptidase (GGT) above normal range and ultrasound signs of liver steatosis) among the study group of patients with at least one metabolic risk factor, to compare it with the control group with no risk factor, to investigate its association with the number of metabolic risk factors and to identify its closest independent predictors.

Methods: Patients with other known liver diseases were excluded. Among 82 patients 52 were in the study group and 30 in the control group.

Results: In the study group the prevalence of ALT, GGT elevation and signs of steatosis was 13.46% (7 patients), 26.9% (14 patients), 36.53% (19 patients), comparing to 6.67% (2 patients), 10% (3 patients) and 5.7% (17 patients) in the control group respectively. The differences were statistically significant ($p < 0.05$). With the increasing number of risk factors we found growing prevalence of GGT elevation and signs of steatosis, but ALT elevation was equally prevalent.

Discussion/Conclusion: Markers of liver disease do have a clinical and prognostic impact on the liver and cardiometabolic risk and therefore we suggest they should be actively screened in this group of patients.

Clinical, functional and morphological assessment of total splenectomy results in liver cirrhosis

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Introduction: Multiple factors can contribute to the development of cytopenia in cirrhosis, but some studies had demonstrated it's reversibility after splenectomy. Our aim was to evaluate the clinical, functional and morphological results of total splenectomy, as a commonly used indication for patients with portal hypertension and hypersplenism in cirrhosis.

Methods: Between January 1998 and December 2009 we enrolled 40 cirrhotic patients with hypersplenism, 16 Child's degree A, 12 Child's degree B and 12 Child's degree C. We evaluated the size of splenomegaly, the peripheral blood cells counts before and 6 months after the treatment, the associated disabilities and the dynamic evolution of hepatic function's parameters. All patients underwent abdominal ultrasonography and endoscopy. The hemodynamic status of spleno-portal system was performed ecographically and the morphologic findings in spleen samples was compared with proven normal spleens.

Results: The most common indications for surgery were anemia (69%) and symptomatic splenomegaly (31%). Splenectomy was performed 2.5 years range after the initial diagnosis. The operation was well tolerated, with only minor complications. The spleen size was significantly higher in cirrhotic patients and correlated inversely with the platelet and erythrocyte counts and splenic macrophages observed had an active phagocytic state. The clinical status of patients was greatly improved after splenectomy. In patients in Child A or Child B classification, the levels of serum albumin and prothrombin time were also improved significantly after splenectomy. The platelet count at 1 and 6 months after the intervention remained in the normal range.

Discussion/Conclusion: Strictly controlled, splenectomy may resolve cytopenia and other complications related to hypersplenism in cirrhosis.

Non-alcoholic steatohepatitis in Bulgarian children: Diagnosis and lifestyle modifications

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Introduction: Non-alcoholic steatohepatitis (NASH) is observed to be increasing among Bulgarian children mainly due to the epidemic of childhood obesity. The aim of the study is to review the clinical and pathological features of pediatric patients with NASH and to assess the therapeutic value of lifestyle intervention.

Methods: This is a retrospective study of 6 patients with NASH (5 males and 1 female), aged 11–17 years, diagnosed between March, 2005–May, 2010. NASH was defined according to the criteria of Brunt et al.

Results: the patients were referred for evaluation of elevated liver enzymes. Obesity was present in 4 children, 2 were overweight. Most of the children had no complaints, 1 of them suffered right upper abdominal pains, 1 was diagnosed with high blood pressure. Only 1 patient had low HDL, all the others had normal lipids and fasting glucose. The median AST was 70 U/L, the median ALT was 120 U/L with a median ratio AST/ALT – 0.5; GGT was slightly elevated – 41 U/L. Increased echogenicity in the liver was noted through ultrasound in all the patients. Histologic liver features were characterized by: severe, mainly macrovesicular steatosis in 2 patients, mild mixed steatosis in 4; portal inflammation was minimal in 4, absent in 2; ballooning degeneration grade 1 was present in all cases; fibrosis was absent in 3 cases, in the other 3 it was distinctively pericellular. All the children and their families were recommended lifestyle changes – appropriate diet, physical activity, support, ursodeoxycholic acid and vitamin E. In the follow up 2 patients showed definite improvement marked with reduction of weight, normalization of liver enzymes and decreased echogenicity. Two children had recurrent episodes of elevated liver enzymes while gaining weight. Two children were non-compliant.

Discussion/Conclusion: Childhood obesity in Bulgaria poses important health problems including NASH. Weight loss through dietary redesign and a regimen of regular exercise remains the mainstay for treatment. We have not found any good effect of drugs.

Platelet count/splenic size ratio could be an important and an independent parameter associated with the presence of esophageal varices

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Introduction: The gastroesophageal varices are a common finding in patients with liver cirrhosis going up to 60% at the first diagnosis. The most feared complication, variceal, bleeding, has dramatic consequences, including death. In Romania, where endoscopy is performed without sedation, there are a number of patients who refuses this investigation. We found important that for those patients to find a non invasive marker who can predict rather aquarately the presence of esophageal varices.

Aim: To evaluate platelet count/splenic size ratio as a non-invasive parameter to predict the presence and absence of esophageal varices in patients with liver cirrhosis.

Methods: We've conducted a prospective study over 2 years (1 January 2008–31 December 2009) included 140 patients admitted in Section II of Institute of Gastroenterology and Hepatology, Iasi diagnosed with liver cirrhosis. These patients were evaluated for the cause of chronic liver disease, ascites and splenic size by abdominal ultrasound, and were made full haematological and biochemical tests The liver function was graded according to Child Pugh score All the patients had upper GI endoscopy to determine if they had esophageal varices and were divided into 2 groups according to presence or absence of esophageal varices and platelet count/spleen size ratio was calculated.

Results: Of the 140 cases: alcoholic etiology in 68 patients (48.57%), the remaining 72 having viral etiology: 54 had anti-HCV antibodies, 16 were Ag HBs positive, 5 have both HbsAg and anti-HCV antibodies and 4 were co-infected HBV + HVD. Cirrhosis were classified in 13 cases (9.28%) in Child-Pugh class A, 68 (48.57%) in Child-Pugh class B and 46 (32.8%) in Child-Pugh class C. Eighty-four (60%) patients had esophageal varices on upper GI endoscopy. The ratio between platelet count/splenic size was found to be significantly ($p < 0.001$) different between patients who had esophageal varices and those who did not.

Discussion/Conclusion: Platelet count/splenic size ratio could be an important and an independent parameter associated with the presence of esophageal varices.

Thrombophilic status in patients with prehepatic portal hypertension (role of genetic and acquired factors)

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Background: The prehepatic portal hypertension due to portal thrombosis was believed to be a rare condition. (about 10% of all cases of portal hypertension). Chronic myeloproliferative disorders (MPD) were considered to be the main cause of thrombotic complications in adult patients. The presence of thrombophilia is considered to be a predisposing factor.

Aim: To study genetic polymorphism of hemocoagulation factors in patients with portal thrombosis.

Materials and methods: 71 patients (26 males, 45 females, median age – 43 years) with portal thrombosis confirmed by Doppler sonography were included into this study. The period from the first manifestation of portal hypertension (splenomegaly, varicose dilatation of esophageal veins) to examination in our Center varied from 1–480 months (median – 82 months).

Only 31% patients had bone marrow morphology of myeloproliferative disorders. The other patients had normal pattern of bone marrow, normal blood picture or cytopenias. All patients were screened for polymorphism of 15 genes of hemocoagulation system, Lupus anticoagulant (LA), homocysteine. All patients were screened for plasma concentration of homocysteine and thrombophilic markers: mutation in gene of methylenetetrahydrofolatereductase (MTHFR), factor V Leiden, prothrombin.

Results: Polymorphisms of genes hemocoagulation system were found in 68% patients. Mutation in genes of methylenetetrahydrofolatereductase revealed in 48% patients (7% – homozygous). The elevated plasma concentration of homocysteine was found in 58% patients, including 48% n patients with MTHFR – gene mutations. Polymorphisms of Plasminogen activator inhibitor-1 gene (PAI-1) – in 58% patients (24% – homozygous), beta-fibrinogen-455 G-A heterozygous – in 34% patients (6% – homozygous). Heterozygous mutations in genes factor V Leiden were found in 2 cases, prothrombin – in 1 patient. 40% patients had polymorphisms of others genes hemocoagulation system, including mutation of integrin alpha II, factor VII, P-selectin (CD 162). The majority of patients (35%) had combination of 3 and more polymorphisms. LA was found in 32% of patients.

Conclusions: The use of molecular diagnostic methods reveals the high frequency of genetic polymorphism of hemocoagulation factors in patients with portal thrombosis.

The presence of the hereditary and acquired thrombophilia proves the necessity of prescribing anticoagulant/antiaggregant therapy in patients with portal thrombosis. In case of hyperhomocysteinemia vitaminotherapy should be prescribed.

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Latent myeloproliferative disorders in patients with prehepatic portal hypertension: Utility of JAK2 mutation

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Background: Myeloproliferative disorders (MPDs) represent a risk factor for thrombosis in the portal vein or its trunks. Portal vein thrombosis may be the first sign of a latent myeloproliferative disorders. The diagnosis of an underlying chronic myeloproliferative disorder (CMPD) is often difficult in patients with primary prehepatic portal thrombosis.

Aim: To study the frequency of myeloproliferative disorders in patients with prehepatic portal hypertension.

Materials and methods: 165 patients (69 males, 96 females, Median age – 43 years) with portal thrombosis confirmed by Doppler sonography were included into this study. The period from the first manifestation of portal hypertension (splenomegaly, varicose dilatation of esophageal veins) to examination in our Center varied from 1–480 months (median 61 months). Most of patients had bone marrow examination and were screened for the JAK2 V617F mutation.

Results: The platelets count increased more $400 \times 10^9/l$ was found in 26% patients, other patients with MPD had normal platelets count and splenomegaly. The bone marrow morphology of myeloproliferative disorders was revealed in 31% patients. The V617F JAK-2 mutation was found in 60% of MPD patients and in 5 patients without clinical and morphological signs of MPD. However, after 1–11 years observation, MPD was diagnosed in all 5 pts and cytoreductive therapy was started.

Conclusions: All patients with thrombosis should be screened for chronic myeloproliferative disorders. Patients with JAK2 V617F mutation should be carefully observed for the subsequent development of overt MPD. In case of MPD cytoreductive therapy with hydroxyurea/alpha-interferon and anticoagulant/antiaggregant therapy should be prescribed for prevention potential thrombotic complications.

Diet and exercise treatment in obese patients with fatty liver disease

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Introduction: The incidence of obese patients with fatty liver has recently increased in Western countries as well as in Romania West side counties. The aim of this study was to evaluate the effects of restricted diet and exercise in obese patients with fatty liver.

Methods: In sixty consecutive obese patients (age 54.5 + 2.9 years, males/females: 25/35) serum levels of enzymes and ultrasonography of liver were evaluated. Obese patients with fatty liver were divided into treated and control group. Forty obese patients followed a program of moderate hypocaloric diet (1250 cal/day) and exercise (walking or gymnastics) for a trial period of 3 months. No changes in diet or life-style were made in control group (20 patients.). Biochemical tests and liver ultrasonography were performed in all patients before and after the trial.

Results: After three months, in the treated group body-weight and serum level of aminotransferases, cholesterol, total lipids and fasting glucose were significantly decreased as well as steatosis (assessed by ultrasonography exam). There were no significant differences in the biochemical findings and liver ultrasound aspects in the control group, before and after trial.

Discussion/Conclusion: Our study suggests that hypocaloric diet and exercise program can improve liver involvement in obese patients with fatty liver disease.

The duplex-Doppler sonography of the liver in patients with metabolic syndrome

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The liver is exposed oneself by harmful metabolic products which influence its function and morphology in patients with metabolic syndrome. The physical examination as well as laboratory tests, do not always answer all questions concerning prognosis and consequences for patients health.

The aim of the study: The comparison of usg picture (duplex-Doppler examination) of the liver and abdominal organs in patients with and without metabolic syndrome.

Patients and methods: 40 metabolic patients and 40 patients without metabolic diseases were examined by duplex-Doppler sonography. Following parameters were estimated by 2D presentation: the liver shape, abdominal organs and vessels size, liver echogenicity. The spectrum size and shape of hepatic vessels flow has been assessed by Doppler presentation. The USG examination was done before and 60–90 min after meal consumption (about 600 kcal).

Results: Metabolic patients were divided into two groups: those without USG abnormalities – 15 patients, and the rest with USG abnormality – 25 patients: gallbladder enlargement, sludge inside enlarged gallbladder, impairment of the gallbladder contractibility, different degree of increased liver echogenicity, focal alteration of the liver parenchyma, enlargement and changes of the liver shape, extension of portal vein confluence, others.

Comments: Following periods of liver damage: steatosis (NAFL) → steatohepatitis (NASH) → fibrosis/cirrhosis are typical stages for metabolic liver damage. Liver biopsy is reliable clinical test for final diagnosis. Numerous USG symptoms are helpful as important clinical test for grade of the liver alteration in patients with metabolic syndrome. Others causes of liver damage should be excluded before.

Conclusions:

1. Considerable group of metabolic patients have normal duplex-Doppler examination of the liver and bile ducts.
2. Numerous usg symptoms allow to assess clinical advancement of liver changes (complications) in metabolic syndrome patients and are helpful for liver biopsy decision.
3. Liver abnormalities observed in duplex-Doppler examination not always are confirmed by clinical tests.
4. Results of the duplex-Doppler examination may constitute important suggestion for therapy and prognosis.

Does leptin-mediate pancreatoprotective effect by activation of HSP in AR42J cells?

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Introduction: Leptin is able to protect the pancreas from the acute damage produced by caerulein-induced pancreatitis (CIP) and its receptors have been detected in the pancreas. Heat shock protein (HSPs) are group of protein, which are produced in the cells subjected to noxious agents and protecting of them from damage. The aim was to investigate the effect of leptin on protein expression of: pro-apoptotic HSP60, 90 and Bax or anti-apoptotic molecules Bcl-2 in the AR42J cells.

Methods: AR42J cells were incubated in standart medium at 37°C for: 0, 3, 12, 24, 48 or 72 h, under basal conditions. Then cells were incubated in presence of increasing concentration of: caerulein (10^{-12} , 10^{-10} or 10^{-8} M), leptin (10^{-8} or 10^{-6} M), or combination of above. Protein expression was detected by using Western-blot and co-immunoprecipitation studies.

Results: Protein expression for HSP60, -90 or Bax and Bcl-2 have been observed in AR42J pancreatic cells under basal conditions. Incubation of AR42J cells in presence of leptin alone resulted in the increase of protein expression for HSP60, -90, Bax and Bcl-2. Caerulein stimulation upregulated the Bcl-2 protein level in AR42J cells, whereas HSP60, -90 and Bax proteins were downregulated. Addition of leptin reversed above caerulein-induced suppression of proapoptotic proteins. On the other hand, leptin inhibited antiapoptotic Bcl-2 protein stimulated by caerulein.

Discussion/Conclusion: Leptin activates HSPs in AR42J cells and this mechanism could take a part in the leptin-induced protection of the pancreatic tissue against acute damage.

Effect of antisecretory factor (AF) on pancreatic amylase secretion *in vivo* and *in vitro*

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Introduction: Antisecretory factor (AF), a protein produced by pituitary gland is expressed in most tissues of human body, including gastrointestinal tract. The plasma level of AF is increased by endotoxins and by certain food constituents. Antisecretory factor has been implicated in the suppression of intestinal hypersecretion and inflammation, but the effects of AF on exocrine pancreas function hasn't been investigated yet.

Aim: To evaluate the effect of intraperitoneal (i.p.) administration of AF on pancreatic amylase outputs under basal conditions *in vivo*, and *in vitro* study, using isolated pancreatic acini.

Methods: The secretory studies were carried out on Wistar rats. The animals were surgically equipped with silicone catheters, inserted into pancreatobiliary duct and into duodenum. Following i.p. administration of AF at doses of 1 or 10 µg/kg, the samples of pancreatic juice were collected in 15 minutes aliquots and the amylase outputs were measured. For *in vitro* study pancreatic acini from intact rats were isolated by collagenase digestion and incubated in presence of increasing doses of AF (10^{-8} – 10^{-5} M) alone or in combination with caerulein (10^{-12} M).

Results: AF at dose of 1 µg/kg i.p. had no impact on pancreatic basal secretion while dose of 10 µg/kg markedly decreased pancreatic amylase outputs. AF (10^{-8} – 10^{-5} M) given to isolated pancreatic acini failed to affect significantly basal amylase release, however caerulein-induced enzyme secretion from pancreatic acini was inhibited by AF in dose-dependent manner.

Discussion/Conclusion: AF could be involved in the physiological decrease of pancreatic exocrine secretion probably by direct inhibition of amylase release from pancreatic acini.

The risk factors involved in the appearance of the pancreatic cancer in patients with chronic pancreatitis

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Introduction: Patients with chronic pancreatitis have an increased risk in developing pancreatic cancer. The purpose of this study was to observe the risk factors involved in the appearance of the pancreatic cancer in patients with chronic pancreatitis.

Methods: We performed an analysis of 174 consecutive patients (63% male, mean age 52.1, range 35–69) with chronic pancreatitis (2007–2009) in the IVth Medical Clinic of University of Medicine and Pharmacy Victor Babes Timisoara. All the patients were diagnosed by clinical criteria, endoscopic ultrasound and CT/MRI by case. It was recorded: age, sex, the alcohol intake (dose, years of drinking), smoking status (number of cigarettes per day, years of smoking). Information about sedentary activities (number of hours sitting down) was also requested from participants.

Results: Pancreatic cancer was found in 15% patients with chronic pancreatitis. The patients with pancreatic cancer were most of them heavy smokers (78%) and heavy drinkers (68%) and had a sedentary life (43%). Participants with one or more first-degree relatives with chronic pancreatitis (19%) showed a higher prevalence of the pancreatic cancer comparative with the rest. The complications of the patients with pancreatic cancer were: pseudocysts (25.5%), obstructive jaundice (10.8%), diabetes mellitus (1.9%), or portal hypertension (2.5%).

Discussion/Conclusion: The results of the study indicated that the patients with chronic pancreatitis and associated risk factors like heavy drinking, heavy smoking or sedentary life developed pancreatic cancer. Pancreatic cancer has a poor prognosis and the best chance for survival is an early diagnosis.

Cholelithiasis in Bulgarian children

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Aim: To assess spectrum and etiology of gallstones in the pediatric patients of a Bulgarian University center.

Methods: A retrospective review of our experience with cholelithiasis between 1987–May, 2010 was done. Data points reviewed included patient demographics, clinical history, laboratory data, imaging studies and treatment options.

Results: The echographic presence of gallstones was noted in 20 patients, of biliary sludge – in 2. Four patients were under 2 years of age, 18 were in the range 5–18. Sex ratio: females:males = 13:9. Fourteen children showed symptomatic course of the disease, presented with colicky pain or typical biliary tract symptoms, 8 were asymptomatic. Their gallstones were diagnosed incidentally on ultrasound examinations for causes unrelated to cholelithiasis. Ninety percent of the children had definitive etiological risk factors, hemolytic disorders predominated. The children under the age of 2 had risk factors associated with immaturity (2) and hemolytic anemia (2). Five adolescents (4 females with non-hemolytic disorder) were surgically treated. Ursodeoxycholic acid was ineffective in dissolution of gallstones in the group of treated children but it had a positive effect on their symptoms. Ten children were followed by expectant management.

Conclusion: In the last years following the extensive use of ultrasound scanning we identified an increased number of children with cholelithiasis. The hemolytic type of the disease is the more common than the non-hemolytic in our center. Adolescent girls with symptomatic gallstones require special attention for complicated disease course.

Primary extranodal non-Hodgkin's lymphomas of gastrointestinal tract

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Introduction: The gastrointestinal tract (GI) is the predominant site of extranodal non-Hodgkin's lymphomas (NHLs). Primary NHLs of the GI tract are rare, accounting for only 1 to 4 percent of malignancies with this localisation.

Methods: During the last 15 years there were registered 19 patients with primary GI NHLs.

Results: The stomach is the most frequently affected parts of the GI 73.68%, being followed by the colonic 21.05% and intestinal localization 10.55%. Histologic 68.42% are extranodal marginal zone B-cell lymphoma of MALT type (E-MZL), 21.05% diffuse large-B cell lymphoma (DLCL), and 10.55% mantle cell lymphoma (MCL). Gross pathology of these tumors differs: a mass or polypoid lesion with or without ulceration in 63.15%, benign-appearing gastric ulcer in 42.1%, nodularity thickened, cerebroid gastric folds in 21.5% of cases and infiltrative lesions in 16%. The majority of lesions are unifocal but 10.55 are multiple extralymphoid determinations. The medium age of the lot is 58 ± 4 years and the sex ratio favor male gender 63.15%. 8 (42.1%) cases are localized stage (IE/IIIE) and 87.5% of this are E-MZ, while only 63.63% of the advanced stages are of E-MZL type. No matter which is the histology and localization primarily symptom was the abdominal pain present in 89.47% of the cases, followed by anorexia in 50% of the cases and weight loss in 30% of the cases. The evolution of symptoms from the debut to the diagnostic ranges from 4 weeks to one year.

Discussion/Conclusion: Despite their rarity, primary NHL lymphomas of the GI tract are important, since their management and prognosis are distinct from that of adenocarcinomas of the GI tract.

Clinical and pathological features of esophageal granular cell tumor – Case report of 10 patients

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Introduction: Granular cell tumors were first described by Abrikossoff in 1926. In 1931, Abrikossoff reported the first granular cell tumor in the esophagus. Granular cell tumor is usually benign lesion located in esophagus and is rarely diagnosed without a histopathological examination. It is more common in men, adults. Recent studies suggest the Schwannian origin of this tumor, positive to S100 protein and NSE.

The purpose of this paper is to present a series of ten cases of esophageal granular cell tumor focusing on the clinico-pathological characteristics and the management according to the current data.

Methods: We report ten cases (8 males and 2 women, age between 33 and 57 years old) discovered incidentally at upper endoscopy. Samples were examined using HE stain, PAS and immunohistochemistry for S-100 protein and Ki-67.

Results: The symptoms are non-specific, unrelated with the esophageal tumors. The lesions are small (4–12 mm diameter), yellow-white, firm consistency, located in the lower esophagus (from 25 cm to Z line). The histology revealed intramucosal and submucosal sheets of polygonal cells, without visible membranes, granular cytoplasm and centrally, small, round nuclei, without visible mitosis and Ki-67 index under 1%. The lesions are non-encapsulated and come into contact with the overlying epithelium. In five cases epithelial hyperplasia was evident. The PAS positive cytoplasm contained abundant eosinophilic granules. Immunohistochemically, there is strong positive cytoplasmic staining for S-100 protein in all cases. Differential diagnosis includes papilloma, squamous carcinoma, xanthoma and ectopic sebaceous glands.

Discussion/Conclusion: The esophageal granular cell tumors are rare, benign, usually sessile nodules discovered incidentally at the upper endoscopy. The control endoscopy performed after the resection of all tumors (3 months–10 years follow-up) revealed no tumor recurrence, which supports the benign character. Accordingly, it is now recommended the endoscopic follow-up of the tumors less than 1 cm diameter, excision being recommended just for cases with dysphagia, tumors over 1 cm, rapid growth, transmural infiltration or suspected malignancy.

High-rate of multiple drug resistance in *Campylobacter* spp. in Ankara, Turkey

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Introduction: The aim of this retrospective study is to determine the frequency of multiple resistance *Campylobacter* spp. in stool specimens of patients with acute diarrhea.

Methods: Total of 2898 consecutive stool samples of patients with gastroenteritis were screened in last five years from 2005 to up to date (60 months period of time) for detection of *Campylobacter* spp. susceptibility pattern in Bayindir Hospital, Ankara, Turkey. Of those 60 identified isolates, 51 susceptibility results were available. The pattern of susceptibility was compared between previous to last 30 months periods.

Results: Results of the antibiotic susceptibility tests of *Campylobacter* spp. by agar dilution method revealed that 68.6% resistance to quinolones and 64% resistance to trimethoprim/sulfamethoxazole and 98% susceptibility to macrolides and 94.2% to tetracycline. Macrolide and tetracycline resistant microorganism strains were susceptible to chloramphenicol. There is no statistical difference in the susceptibility patterns when comparing the two 30 months period of time.

Discussion/Conclusion: Specifically, macrolide group antibiotics and tetracyclines should be the first choice of drugs in the treatment of *Campylobacter* gastroenteritis. On the other hand, because of high tetracycline resistance in other bacteria involved with acute gastroenteritis, not the quinolones nor tetracyclines but macrolides seem a better alternative in the treatment of empirical initiation of antibiotic therapy in community acquired diarrhea.

Acute effects of exercise intensity on appetite, food intake and release of gastrointestinal peptides

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Introduction: There is still uncertainty regarding the effects of different types of exercise on appetite and food intake. Thus we sought to investigate the acute effects of exercise on appetite subjective sensations, food intake and gastrointestinal peptides release.

Methods: Twelve young men took part in following tests: low-intensity exercise (LIE) on a cycle ergometer, higher intensity exercise (HIE) above the aerobic anaerobic threshold, sedentary study (SS) followed by ad libitum test meal. Blood samples were obtained and ghrelin, insulin, gastrin, lactate and glucose plasma levels were evaluated. Additionally subjects rated their subjective feelings of hunger and prospective food consumption.

Results: Energy intake at the test meal was significantly higher after the exercise when compared with the control group. Hunger or motivation to eat ratings were decreased in response to exercise but only in HIE changes were statistically significant. In the control group without meal test plasma ghrelin levels increased steadily from 148.3 ± 18.8 pg/ml to 173.7 ± 54.1 pg/ml at end of the experiment. In group with test meal ghrelin decreased in postprandial period to 107.3 ± 12.3 . In response to LIE ghrelin rose by about 40% and decreased thereafter. During the HIE intervention ghrelin did not change but fell in postprandial period by about 30%. A trend towards a decline of plasma insulin levels during the LIE and HIE was observed while meal intake caused a rapid increase. Despite a tendency for higher gastrin levels during the HIE, they did not reach statistical significance.

Discussion/Conclusion: Acute exercise temporarily suppressed hunger and motivation to eat sensations but food intake was augmented in these conditions. The present data suggest that low rather than high-intensity exercise stimulates ghrelin release. The impact of exercise on appetite and subsequent energy balance could not be fully explained by changes in plasma ghrelin.

Role of the psychogenic and social factors in children with recurrent abdominal pain

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Introduction: Recurrent abdominal pain (RAP) is one of the most often complaint of children. We consider as children with RAP all patients suffering at least once per week for two consecutive months per year.

Aim: The objective of this work was to analyze how great is the role of psychosocial factors in RAP comparing with the role of *Helicobacter pylori* infection and endoscopic changes. The second problem is relationship between inflammatory disorders and somatization of emotions. The third question is if the psychosocial factors may be the base for RAP and recognition of functional disorders.

Methods: The study comprises 133 children aged between 6 and 16 years with the symptoms of RAP. The routine diagnostic algorithm searching for structure and

function-originated disease was carried out. Our protocol included: biochemical examinations, ultrasonography, endoscopy of upper digestive tract with histopathological confirmation and psychological consultation. Among psychogenic factors the neuroticism test, school phobias, family problems as alcoholism of parents and interpersonal relations were taken under consideration.

Results: We stated *H. pylori* infection, different level of endoscopic changes and positive psychosocial factors in 29 children (21.8%). In 34 cases (25.6%) psychosocial problems were observed together with endoscopic findings without positive urease test. 10 (7.5%) patients with and 24 (18%) patient without *H. pylori* infection had only endoscopic changes. Psychological consultation was positive in 24 cases (18%) as the only reason of RAP.

Discussion/Conclusion: The analysis suggests that about 65% of children with RAP reveals influence of psychogenic factors on symptoms. Psychogenic problems may coexist with another reasons of RAP. The result of treatment depends on common work of physician and psychologist.

Different effects of food contaminants – Mycotoxins fumonisin B1 and B2, on cell proliferation in the digestive tract

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Introduction: Fumonisin B1 (FB1) is a mycotoxin produced by the fungus *Fusarium moniliforme* that contaminates corn. Fumonisin B1 (FB1) causes the human oesophageal and liver cancer. Fumonisin B2 (FB2) is less abundant but may modulate FB1 effects. Fumonisin B2 (FB2) may amplify the hepatocarcinogenic effect of aflatoxins. We previously demonstrated that FB1 disrupted the colon microbial ecosystem. Now we present new data on different regulation of cell proliferation by FB1 and FB2 that may refer to its carcinogenic potency.

Methods: In vivo, FB1 and FB2 were added per os to C57Bl/6 mice (0.01–1.0 mg/kg body weight). At the end of experiments, the liver, intestine, colon, Payer patches were removed, tissue were stained for immunohistochemistry, cells were separated, stained by antibodies, and analyzed by flow cytometry. In vitro, FB1 or FB2 were incubated with cells from intact mice liver, colon, and intestine. Signaling proteins were analyzed by Western blotting and flow cytometry.

Results: in vivo and in vitro, FB1 and FB2 had diverse effects on the upstream inhibitors of kinase mTOR signaling pathways regulating protein synthesis and cell proliferation. Low doses of FB2 caused the arrest of cell proliferation and apoptosis induction. FB1 increased the cell proliferation and inhibited an apoptosis. Regulation of downstream proteins from mTOR signaling pathways were different under FB1 and FB2 exposure. Simultaneous exposure of both FB1 and FB2 in different composition resulted in modulation of signaling pathways connected with cell proliferation and apoptosis.

Discussion/Conclusion: Contamination of food by mycotoxins fumonisins B1 and B2 modulate the cell proliferation and creates the basis for amplification of carcinogenic potency of other nutrient-dependent compounds

Immunoexpression of the vascular marker CD31 in endothelial cells of microcirculation in the oral soft tissues in prosthetic patients with titanium implants subjected to extremely low frequency magnetic fields

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Introduction: Modern dentistry willingly takes advantage of new methods that contribute greatly to conventional treatment; intra-osseous implants combined with extremely low frequency magnetic fields (ELF MF; syn. magnetostimulation) with induction similar to Earth's field are gaining an increasing interest. However, the sequence of morphological events concerning the oral vascular bed following of such therapy has not been yet presented. Study objective was microscopic assessment of angiogenesis, with special regard to the immunoreactivity of the endothelial marker CD31, in soft tissues covering the alveolar process after stimulation of ELF MF with low value of induction in patients with intra-osseous titanium implants.

Methods: The immunohistochemical (IHC) investigations involved 19 patients qualified for surgical-prosthetic procedures in order to prepare the bed for the titanium implant Alpha-Bio. Each patient underwent necessary surgical incision and a full-thickness flap covering the mucosa and periosteum was prepared. The collected material was routinely stained (H,E) and immunohistochemically for CD31 factor (with monoclonal mouse antibody, DAKO, Clone JC 70). One day after the surgical procedure, the same patients were subjected influence of ELF MF using the Viofor JPS system according to the therapeutic program M1P3, 30 procedures altogether. Specimens for analysis after application of magnetostimulation were collected during gum correction and implant exposure procedure.

Results: IHC investigations for the angiogenesis marker CD31 by far better than routine staining with H,E identified the network of microcirculatory blood vessels in the soft tissues covering the alveolar process in patients with intra-osseous titanium implants subjected to magnetostimulation. They also greatly contributed to the assessment of the sequence of morphological events observed in the process of angiogenesis. CD31 labeling indicates that the exposure with ELF MF of low induction markedly stimulates angiogenesis and widens the vascular bed in the studied oral soft tissues.

Discussion/Conclusion: Application of ELF MF, due to a better blood supply, may significantly accelerate regeneration processes in the soft tissue covering the alveolar process. It may also enhance bone union processes, which altogether could explain the beneficial effect of the therapy applied on the healing of the intra-osseous implant of Alpha-Bio type.

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