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CONFERENCE PROCEEDINGS

Highlights in mechanisms and therapies for gastrointestinal and hepatic diseases: 1996 Shanghai International Gastroenterology Conference

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The 3rd session of the Shanghai International Gastroenterology Conference was held on November 28-30, 1996 in Shanghai under the auspices of president Dong XS and co-presidents Tytgat GNJ, Kurihara M and Owyang C. Top quality state of the art lectures were given by many top experts on all aspects of gastroenterology and hepatology, from the United States, United Kingdom, Australia, Canada, Netherlands, Germany, Japan and other European and Asian countries, as well as from all parts of China. Many basic and clinical research papers were presented, focusing on current concepts and recent developments in these fields. Only the most important and fascinating advances will be discussed here.

A new concept has been devised about the mechanism of acupuncture action on the gastrointestinal tract by Hunt RH (Canada), the efficacy of which is through the action of endogenous opioids and other neural pathways to regulate gastrointestinal motor and secretory function and the gut brain axis. The effect is negated by naloxone, which further supports the involvement of central opioids in this mechanism. Gastroesophageal reflux disease has been defined primarily as a motor disorder. Reflux events are associated with transient relaxation of LESP, esophageal clearance abnormalities and occasional failures in gastric emptying. Refluxate containing acid and peptic activity can lead to mucosal damage. GERD can be relapsing with recalcitrant symptoms and motor disturbance. Long-term proton pump inhibitors are necessary (Tytgat GNJ, Netherlands). Approximately 50%-60% of cases of non-ulcer dyspepsia are associated with CagA toxin-produced *H. pylori* gastritis. About 50% of patients with NUD experience pain or discomfort with balloon distention of the gastric fundus and whether or not this visceral hyperalgesia is related to psychological stress is still to be investigated. With the eradication of *H. pylori*, symptoms of NUD will improve and become asymptomatic one year later (Lam SK Hong Kong). It is known *H. pylori* infection is related to gastric cancer. Farthing MJG (London) found that *H. pylori* can cause disruption of the intercellular cytoskeleton and perturbation of the tight junction of gastric epithelial cells, leading to epithelial permeability alteration. Epithelial cells infected with *H. pylori* produced IL-8, a neutrophil chemotactic enhancing inflammatory cascade. The ammonia liberated also inhibits gastric cell growth in the S phase, thus progressing to atrophy, involving the antrum or even the corpus, then metaplasia and dysplasia occur and finally carcinoma. The inflammation and oxygen free radicals liberated lead to a hyperproliferative state and an extrinsic diet deficient in antioxidant vitamins may contribute to promoting the neoplastic process. Ming SC (Philadelphia) claims that the carcinogenesis of GI cancer primarily follows two routes: (1) chronic inflammation, epithelial hyperplasia, metaplasia, dysplasia, carcinoma; and (2) metaplasia, adenoma, increasing dysplasia and carcinoma. Carcinoma involves the alteration of many genes which variably regulate cell growth, cell differentiation, cell death, DNA repair and intracellular adhesion, as well as mutational changes in oncogenes, tumor suppressor genes and genes related to invasion and metastasis. Growth factors and their receptors, stromal cells and inflammatory cells also contribute to the growth of cancer. Various GI peptide hormones have been investigated regarding the growth of gastric, colonic and pancreatic cancers (Chen YF, Beijing). Bombesin has been to found to exert an autocrine regulatory effect on cell growth in human gastric epithelial cells. Vasoactive intestinal peptide stimulates the growth of pancreatic and colonic cancer cell lines which express the VIP receptor and the antagonist of the latter inhibits VIP-promoted cancer cell growth. Cholecystokinin stimulates the growth of human pancreatic carcinoma cells and this effect can be inhibited by the CCK receptor antagonist, proglumide. Finally, somatostatin has been found to inhibit EGF promoted cell growth in human gastric cancer and human hepatoma cell lines, all of which express EGF receptors. The signal transduction pathways are still to be elucidated. A lysosomal cysteine protease, cathepsin B, has been implicated in the progression of human and rodent tumors and positive tumor cathepsin B staining is correlated with the depth of invasion. The clones with a high metastatic potential show a higher expression of cathepsin B than those with a low metastatic potential. The level of cathepsin B mRNA is increased in GI cancer and plays a significant role in GI cancer progression (Ren WP, Shanghai).

β-carotene in its physiological amount of 5 mg/d, Vitamin E and selenium have been shown to lower stomach cancer incidence significantly during a 5 year period. However, large supplements of 30 mg/d with 2500 IU of vitamin A/D, owing to its nonspecific oxidation cleavage, produce metabolites as beta-apo-carotenal aldehyde and beta-apo-carotenoic acids which, in conjunction with heavy smoking or asbestos exposure, lead to lung cancer (Russel RM, Boston). Parvovirus HI has been proved to suppress tumor growth of human epithelial cells in immunocompromised recipient mice. The mechanism of parvovirus-induced oncosuppression is believed to be oncolysis. The viral protein NS-1 is likely to have a major effect, its cellular cofactors or targets undergo transformation-triggered modification and it is required for toxicity (Rommelaere J, Germany).

H. pylori infection leads to persistent hyperproliferation of gastric epithelial cells, causes chronic gastritis and gastric atrophy and is associated with both proliferation and apoptosis of the gastric epithelium. The decreased acid secretion might result in changes of the gastric bacterial flora and promote the nitroso compounds causing gastric bacterial flora and gastric carcinogenesis (Liu WZ, Shanghai). Kurihara M (Japan) advocates a combination of 5 DFUR, CDDP and a derivative of camptothecin, CPT-Ⅱ to treat late gastric cancer, which can raise the effective rate to 43%. Preoperative chemical or chemoradiotherapy and postoperative intraperitoneal chemotherapy are currently under consideration as a new strategy for prevention of micrometastasis, so as to increase curative resection of gastric and esophageal cancer, but this is still controversial (Ajani JA). Early and radical resection of gastric cancer yielded a 5 year survival rate of 49.2% (355/803) in the period of 1984-1991 in Shanghai Rui Jin Hospital, better than 32.6% (383/1175) during 1958-1983. Cooperation between gastroenterology endoscopists and surgeons played a key role (Lin YZ, Shanghai). Folic acid supplements are recommended to decrease the recurrence rate of colorectal adenomatous polyps after removal because a diminished folate status promotes carcinogenesis, folate deficiency induces p53 specific strand breaks in colonic mucosa and DNA strand breaks and genomic DNA hypomethylation participate in the evolution of neoplastic transformation. Induction of strand breaks creates a chromosomal aberration and increases the mutation rate of critical cancer associated genes and the development of neoplastic transformation. A 5-6-fold supplementation of folic acid might give the opposite effect (Mason JB, Boston). Familial adenomatous polyposis and hereditary non polyposis colorectal cancer genes have been identified and gene testing to search for the gene carrier in affected families is now available commercially. Fecal occult blood tests and colonoscopy once every 1-2 years are recommended for all adults, starting at the age of 50 years (Burt RW, Utah).

For the treatment of inflammatory bowel disease (Singleton JW, Denver, United States), 5 ASA and glucocorticoids are still the most effective drugs to achieve remission in Crohn's disease and ulcerative colitis, with immunosuppressants such as 6 mercaptopurine, azathioprine or methotrexate resulting in remission for both diseases. Metronidazole and ciprofloxacin are also adjuncts for Crohn's disease. TNF antagonists and bradykinin antagonists are currently being explored in IBD.

A metastatic model of human HCC in nude mice has been developed, with 100% intrahepatic, lung and lymph node metastasis after 30 generations showing invasiveness of HCC related to certain oncogenes and growth factors, including p16, p53 mutation, H-ras, c-erbB-2, TNF-α, EGF receptor and MMP2, but not nm23-H1 and TIMP2. Antisense H-ras and anti HBx antibody plus LAK cells can inhibit cancer growth in that model. *TNF* gene liposome intralesional administration also had an inhibitory effect in the HCC model in nude mice (Tang ZY, Shanghai). Treatment of chronic hepatitis B has been advanced by developing new antiviral agents, such as lamivudine and famciclovir which act as reverse transcriptase inhibitors and HBV DNA polymerase inhibitors, respectively. Both of these drugs can produce a profound decrease in serum HBV DNA levels within 12 wk of treatment but very few patients cleared HBeAg, with a current study indicating that prolonged usage is necessary for a sustained effect. Clinical trials of synthetic peptide vaccines containing cytotoxic T cell epitopes for HBcAg and DNA vaccines with recombinant HBV surface gene are underway, showing promising results (Lok ASF, Michigan). For compensated liver cirrhosis due to chronic hepatitis B, a high protein vegetarian diet combined with acyclovir and ribavirin resulted in a negative to positive nitrogen balance, with 30% HBsAg, 25% HBcAg and 33% positive HBV DNA becoming negative at the end of the treatment (Tang ZD, Shanghai). Tropical chronic pancreatitis is common in southern India, characterized by recurrent chronic abdominal pain, insulin dependent diabetes and large pancreatic calculi affecting young male adolescents. Malnutrition, protein deficiency and an impaired immune response are believed to play an etiological role. High doses of insulin, analgesics for pain and pancreatic enzymes are necessary for control and surgical decompression of a dilated pancreatic duct with removal of pancreatic stones, resulting in improvement in both endocrine and exocrine insufficiency, as well as pain relief. Sphincterotomy, fragmentation of stones with subsequent removal and pancreatic stenting have also been effective (Tandon RK, India). In acute hemorrhagic necrotizing pancreatitis, target treatment with liposomes of proglumide and emodin in a rat model showed a significant increase of autophagy and autophagic vacuoles within which organelles were seen on ultramicroscopy. Thereafter, the autophages decreased in number and size. It is believed that emodin has a stabilizing effect on the lysosomal membrane and a direct effect in the pancreas, which differs in its mechanism of action from that of somatostatin (Xu JY, Shanghai). Patients with irritable bowel syndrome have visceral hypersensitivity and the visceral perception is via activation of afferent pathways by stimulating mucosal receptors, smooth muscle mechanoreceptors and mesenteric nociceptors. Trivial physiological stimuli can induce pain and those with diarrhea and rectal urgency experience diffuse abdominal pain, whereas healthy subjects only note discomfort localized in a single quadrant. Abnormal psychological features are also found. Bulking agents should be given to those with constipation, whereas those with diarrhea can have octreotide or the 5-HT-3 receptor antagonist fedotoxine which blunts perception of visceral distention (Owyang C, Michigan). A series of western medicines, colchicine, polyunsaturated lecithin, IFN-γ, retinoids, *etc.*, to treat hepatic fibrosis were reviewed by Wang BE (Beijing), with a special emphasis on the use of herbal medicine compound 861. Both animal experiments and clinical B hepatitis patients showed a significant attenuation of inflammation and fibrosis, stimulation of collagen degradation, less synthesis of total and type Ⅰ, Ⅲ and Ⅴ collagen, less mRNA expression for procollagen Ⅰ, Ⅲ and Ⅳ in liver tissue and also inhibition of TGF-β, in which collagenase activity was increased and TIMP activity decreased. Diabetic gastroparesis may exhibit myelin degeneration of the vagus nerve or be associated with impairment of sympathetic nervous function. There is also decreased smooth muscle contractility with a biochemical abnormality at the smooth muscle cell level. Prokinetics such as metoclopramide, domperidone, cisapride and erythromycin have their nature and sites of action delineated (Wiley IW, Michigan).

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