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Sendai, Japan, March 24–26, 1988
Chairman: Toshio SATO, M.D.

Symposium-1

Technological advances in the diagnosis and treatment of digestive diseases

Moderators: Takenobu KAMADA and Yasuo IDEZUKI

Computer-assisted image processing in electronic endosocopy

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Progress in medical engineering enabled to estimate the tissue hemodynamics directly in human. In this symposium, we reviewed the recent developments in image analyses and spectrophotometry in digestive endoscopy.

(1) Organ reflectance spectrophotometry (ORS)[1]: Digestive organs contain various pigments such as hemoglobin (Hb) and cytochromes. These pigments can be estimated from the reflectance spectra of organ obtained through an endoscope using optical fiber noninvasively. Using ORS, we have revealed that tissue hemodynamics, oxygen metabolism and intracellular redox level play important roles in development and healing of various digestive diseases in human.

(2) Spectroscopy using electronic endoscopy: Using the computer-assisted image analyzer, the index of mucosal Hb concentration ([Hb]) was processed from the electronic endoscopic picture as previously reported[3,4]. The processed index (k*logVr/Vg) correlated well with [Hb] determined in vitro and in vivo and mucosal blood flow by H_2 gas clearance technique. The analysis of mucosal hemodynamics in 13 patients with gastric ulcers and 5 normal subjects suggested that the hemodynamic changes play important roles in ulcer healing. Moreover, the automatic image analysis of gastric mucosal hemodynamics using electronic endoscopy was useful to evaluate ulcer healing. The method to obtain the tissue oxygenation directly from the near-infrared electronic endoscope was also discussed.

(3) Infrared electronic endoscopy: As reported previously[4], two infrared illuminations were made; one was reflection type from luminal side and the other was transmission type from outside of the body. The infrared light was caught by CCD of the endoscope located inside the stomach. Using this system, the vascular abnormalities in gastric wall can be analyzed in patients with gastric diseases.

To make endoscopic diagnosis more objective, we have developed the methods to evaluate various morphologic characteristics and tissue functions quantitatively. Developments of new technology, such as image processing contribute to the progress in quantitative endoscopy.

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Diagnosis of liver diseases by imageing techniques with computer

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Anatomical surface of the liver, spleen, gallbladder and/or hepatoma was demonstrated as the three-dimensional image by computer-graphics technique. These images were reconstructed from organ-surface information derived from computerized tomographic scans and displayed as wire-frame and or solid models on a color CRT. In liver cirrhosis, atrophy of the right lobe, hypertrophy of the left lobe, and splenomegaly were vividly apparent. In hepatoma, three-dimensional intrahepatic location of hepatoma was easily recognized. Furthermore, hepatic artery was displayed as solid model. It is thus expected that this system will prove clinically useful in the noninvasive evaluation of patho-morphological changes in the liver and spleen.

On the other hand, portal hemodynamics was evaluated by single photon emission CT (SPECT) and ultrasonography. SPECT was performed for the intra-abdominal blood pool with ^{99m}Tc autologus red blood cells. Portal vein and portosystemic collaterals were clearly observed in coronal images. These images were well consistent with images obtained by scintiphotosplenoportography or arterial portography. However, SPECT iamges provide no information about the direction or velocity of the blood flow. We also used the real-time two-dimensional Doppler echography. By this method, color flow mapping of the portal vein, splenic vein and/or coronary vein was obtained. Therefore, the combined use of SPECT and Doppler echography permits the qualitative and quantitative evaluation of portal hemodynamics noninvasively.

Analysis of digestive tract cancer by use of monoclonal antibodies and cDNA probes and their clinical application

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We have developed two unique monoclonal antibodies which are able to detect tumor-associated antigens in the sera from patients with adenocarcinomas such as pancreas cancer and stomach cancer[1]. Sandwich enzyme immunoassay revealed that the incidence of abnormal antigen YH206 levels was 34% and 44% in stomach cancer and pancreas cancer, respectively, and that the incidence of abnormally higher levels of antigen MUSE11 was 32% and 63% in stomach and pancreas cancer, respectively. Since these antigens are different from CA19-9 antigen and from other reported antigens, these novel antigens may be used as additional tumor markers for seroimmunodiagnosis of stomach and pancreas cancers. In order to study the change of *ras* oncogene product p21 in various cancer and precancerous lesions, we have generated monoclonal antibody rp12 (IgM) and rp38 (IgM). Immunoperoxidase staining with this monoclonal antibody revealed that the incidences of positivity of p21 (ras) in each case were 72% (28/39), 58% (19/33) and 0% (0/9) in colon carcinoma tissues, colonic adenomatous polyps and morphologically normal tissues, respectively. These data suggest that the expression of p21 (ras) may be enhanced in the premalignant lesion such as colonic adenomatous polyp.

A cDNA probe for CEA was used for detecting mRNA in the various tissues. Some lesions with interstinal metaplasia showed positive reaction, whereas noncancerous gastric or colonic mucosa exhibited negative staining.

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Protein bioengineering for designing enzyme-peptide therapeutics

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Owing to the recent acvance in biomedical science, molecular mechanisms for various diseases have been clarified. Hence, biospecific enzymes and peptides have been tested for their ability to be ideal therapeutics for various metabolic deseases. Recent studies on protein chemistry and genetic engineering enable one to obtain large amounts of enzymes, peptide hormones and their analogues whose physicochemical and immunological properties are more suitable for clinical use than those of natural origin. However, clinical use of these compounds has been highly limted predominantly due to their biological instability and unfavorable behavior in vivo, such as rapid elimination by renal glomerular filtration and removal by reticulo-endothelial systems.

To establish a method for controling behavior of protein-peptides n vivo, we synthesized several enzyme derivatives of human-type superoxide dismutase (SM-SOD) and bilirubin oxidase of bacterial origin (PEGBO) by linking bydrophobic organic anions with high affinity for a albumin and polyethylene glycol with low immunogenicity, respectively. SM-SOD circulated bound to albumin for extremely long time, accumulated in an injured site of a tissue whose local pH was decreased by metabolic perturbation, and efficiently protected cells against reactive-oxygen toxicity elicited in various diseases, such as ischemic myocardial injury, brain edema, stress-induced gastric ulcer, etc. In contrast, unmodified SOD rapidly disappeared from the circulation and, hence, revealed no such protective action. PEGBO also circulated with much longer half life (3h) than the native enzyme (2.5 min) and markedly decreased plasma bilirubin levels of jaundiced Gunn rats, Dubin-Johnson model rats, and in bile-duct-ligated control rats; immunoreactivity of PEGBO with specific antibody against its proteinous domains was extremely lower than the unmodified oxidase. Based on such experiments, a novel strategy for molecular designing of protein-peptide therapeutics was proposed.

Photoradiation diagnosis of malignant tumors

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We attempted to make a diagnosis for the detection of malignat tumors using photoradiation with eosin yellow (eosin Y) as a photosensitizer.

Materials and Method: The subjects consisted of 21 patients (18 male, 3 female) who were diagnosed with esophageal cancer. All the cases of esophageal cancer were diagnosed histologically as squamous cell carcinoma. Concerning the method, eosin Y (10mg/kg) was administered 48 hours before the operation via a 2 hour intravenous drip infusion. The lymph nodes, which had been excised during the operation, were then placed in the bottom of a cylindrical column, and exposd to argon laser beam (wavelength: 514.5nm, power: 400-800mW) from a distance of 15 cm apart in a dark box.

Results: Fluorescence in the cancerous lesion was observed in all 19 patients examined. A total of 103 lymph nodes were extirpated during the operation. Of these, 42 lymph nodes exhibited fluorescence, but only one revealed no metastasis. For the false positive result, it was assumed that the reflection of the laser beam could be assessed as light emission. Among the remaining 61 lymph nodes, which did not exhibit fluorescence only one of these revealed metastasis. For the false negative result, it was assumed that the laser beam did not radiate the focus of malignant cells, because the malignant cells were too small.

This procedure proves to be beneficial for detecting metastatic lesions of esophageal cancer.

Innovative laser therapy by advanced manufacturing technology on quartz fiber tip

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Nd YAG laser has been used for treating cancers endoscopically due to its properties of good propagation in the water and of good tisse coagulability. We have been developing new therapeutic methods utilizing the characteristics of this near infra-red laser.

(1) Spherical radiaton method: Applying double conical shape with a round nose on a tip of a quartz fiber, uniform and spherical radiation became possible. In-depth continuous laser radiation gave spherical coagulated tissues in the liver corresponding to the beam pattern. After fundamantal studies such as analyses of time lapsed charges of tissues coagulated, multiple points measurements of in-depth temperature of the tissues radiated and development of gas evacuation devices, clinical procedures were implemented successfully. Coagulasted tissues in 5 cm could be got in short time laser radiation with no serious complications. Perctaneous hepatic approach was available in case of poor risk patients.

(2) Lateral radiation method:The lateral laser radiation probe with the truncated tip was developed. It provided reasonable total reflected radiation by 60 degrees. Free rotability attained by applying micro coil springs actualized endoscopical lateral radiation therapy. In the combination with a side-viewing endoscope or with a forward-viewing one, any diseases on the walls of hollow organs have been successfully treated. "Circulating water balloon" laser radiation method through thin latex balloon filled with water could successfully coagulate canine mesentric veins without rupture in length by delivering continuous laser energy. Controlling the temperature of circulating water in the balloon lead to outstanding changes of features coagulated. This method of coagulation depth control will provide much higher probability of radical cure of laser therapy by the combination of the endoscopically deliverable ultrasound probe.

Diagnosis of diarrhea with potential difference of the small intestine

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Since there was no effective method for evaluating the absorptive capacity in the small intestine of patients with severe diarrhea, we devised a test for evaluating the absorptive capacity with potential difference. In our experiments of guinea pigs, potential difference by sugars or neutral amino acids ingestion accurately reflected their real flux under condition with malabsorption. In clinical cases, the double lumen tube with an electrode was inserted and positioned in the jejunum. A standard solution and test solutions were perfused and the potential difference was recorded with a DC recorder. In the infants with short bowel syndrome, values of sugar-or amino acid-evoked potential were normal range of slightly low except one case whose potential differences were twofold. In the patient suspected of having glucose-galactose malabsorption, jejunal perfusion of D-glucose or maltose evoked no change in the potential difference. This method is useful to examine absorptive capacity, for example, Vmax and Km, and to make a diagnosis without worsening of patients conditions.

Symposium-2

Endotoxin related digestive disease

Moderators: Kyuichi TANIKAWA and Kenji KOYAMA

Advances in limulus assay and clinical significance of endotoxemia

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Limulus gelation test (LGT) has been employed as the preferable assay to detect endotoxemia. Recently, however, Iwanaga improved LGT by two steps. Firstly, he developed limulus colorimetric test (LCT) which enabled us to determine blood endotoxin level quantitatively at pg/ml order. Secondarily, he clarified the mechanism of false-positive response by β-glucan and developed endotoxin-specific (E-S) test using recombined limulus coagulation enzymes. Consequently, LGT-positive responses have been classified into three groups. These are septic endotoxemia resluting from gram-negative septicemia, false-positive responses due to β-glucan and non-septic endotoxemia seen in hepatic failure and after resection of the cirrhotic liver. Non-septic endotoxemia has a positive-response in conventional LCT but a negative-response in E-S test, quite similar to β-glucan. We think it is an urgent problem for the study on endotoxemia to reveal the nature of non-septic endotoxemia.

Study of the relationship between endotoxin and hepatic injury in alcoholic hepatitis and hepatitis type A

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The aim of the present study is to elucidate the role of endotoxin in the pathogenesis of liver dameges in alcoholic hepatitis and hepatitis type A.

Endotoxemia detected by limulus amoebocyte lysate test was frequently found in acute phase of alcoholic hepatitis and hepatitis A; 42.3% of alcoholic and 41.2% of hepatitis type A respectively. Circulating immune complex was also frequently detected in these patients. Remarkable elevation of serum immunoglobulin M (IgM) is a characteristic feature of hepatitis type A. Serum levels of IgM class anti-Lipid A antibody during acute phase were significantly higher in patients with hepatitis type A than those with type B. Under the electron microscope, the Kupffer cells located at the periportal area were remarkably enlarged and filled with distored organelles and electoron dense lipofusion-like lysosome, containing neumerous hepatitis A virus particles. These results suggest that the reticulo-endotherial system of the liver is markedly dameged in hepatitis type A.

IgA class anti-Lipid A antibody measured by ELISA was frequently found in patients with alcoholic hepatitis. Polymeric IgA containing anti-Lipid A antibody has been observed in the serum obtained from alcoholics. Cultured rat Kupffer cells treated with ethanol showed reduced number of cytoplasmic projection and depression of phagocytosis of latex particles. These results suggest that alcoholic hepatitis had depressed reticulo-endotherial system which result in endotoxemia. Consequently, these results suggest that endotoxin play an important role in the pathogenesis of hepatic injury hepatitis type A and alcoholic hepatitis.

Realtionship between endogenous endotoxemia in cirrhotic patients and complications of cirrhosis, and treatment of these endogenous endotoxemia

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Endotoxin was studied by Limulus lysate test, and by endospecy test in ascites and in plasma of the 62 cirrhotics with both ascites and esophageal varices, and in plasma of the 63 control cirrhotics with esophageal varices only. Endotoxin was positive in 38 (61.3%) of ascitic fluid and in 40 (64.5%) of the plasma in the cirrhotics with ascites. In contrast, it was found in 36.5% (23 of 63) of the control cirrhotics. Death occured within 6 months in 50% of the patients with endotoxemia, whereas only 14% of those without endotoxemia ($p<0.05$). The concentration of total protein in ascitic fluid of the patients with endotoxemia (1.4 ± 0.7g/dl) was nearly twice as high ($p<0.01$) as in patients without endotoxemia (0.7 ± 0.4g/dl), suggesting the endotoxemia may be a precipitating factor in the formation of ascites. The frequency of rupture of esophageal varices (within 6 months) in cirrhotics with more than 2 (+) positive Limulus assay (11 out of 21, 52%), was significantly higher than that of the patients with less than 1 (+) Limulus assay (7 out of 28, 25%). Endogenous endotoxemia in cirrhotics disappeared by the administration of diuretics, lactulose, and of paromomycin sulfate (non-absorbable antibiotics).

Endotoxemia in gastroenterological surgery

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Endotoxemia remains a principal cause of death after major operative procedures. During 13 years, from 1975 to 1987, endotoxemia occurred in 54 patients with postoperative complications. Of these 45 (83.3%) were infectious diseases. Nine were intestinal obstruction and superior mesenteric artery occlusion of endogenous endotoxin.

Rats given an entotoxin were prepared 3 and 5 hours after induction of peritonitis by cecal incision. Changes in glucose metabolism in the livers of rats were studied with assays of glycolytic intermediates, radioprecursors oxidation and glucoregulatory enzyme activities. Glucose-6-phosphate and fructose-6-phosphate were found to be significantly decreased, while fructose-1,6-diphosphate, pyruvate and lactate were increased. In the liver slices, the conversion of ^{14}C-glucose to labeled $^{14}CO_2$ increased compared to the control animals, while ^{14}C-glutamate conversion to $^{14}CO_2$ markedly decreased. Activities of phosphofructokinase and pyruvatekinase which are regulatory enzymes in glycolysis were significantly increased 3 hours after the induction of peritonitis. The activity of fructose-1,6-diphosphates, increased compared to the control value. These findings suggest that glucose consumption appears to be increased, but TCA cycle activity, which was assessed by glutamate oxidation, appears to be decreased in the livers of rats induced with peritonitis.

These absorption routes of endotoxin derived from the intestine, via portal vein, via intestinal lymphatics and via transperitoneal routes have been studied. As the various intestinal obstructions, a simple obstruction, a strangulated obstruction, SMAO and SMVO were induced. The levels of portal vein endotoxin gradually increased. The level of endotoxin that seeped through the intestinal wall showed and increased. In the SMAO and SMVO, endotoxin levels in lymph from the thoracic duct were significantly high.

An experimental sudy on the cholestatic effects of continuous low-dose endotoxin administration

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Cholestatic jaundice without any obvious mechanical biliary obstruction is often seen in the patients with gram-negative sepsis. This experimental study was performed to examine the cholestaic effects of continuously infused low-dose endotoxin (LPS).

Donryu rats weighing around 450gr were placed tubings in jugular vein and common bile duct. The former tubing was for continuous administration of LPS, the latter was for bile collection. LPS was infused continuously at the rate of 0.0295 mg/body/hour for 24 hours, whereas the same amount of saline to control rats. Blood pressure and hepatic blood flow were monitored in a part of LPS group animals and showed no significant change during LPS infusion.

LPS group showed significant reduction of bile output compared to control group during the period from 7.5 to 15 hours of continuous LPS administration. Serum total bilirubin level was significantly increased in LPS group with direct bilirubin accountig for more than 75%. Regresson analysis between bile output and bile acids output suggested that the inhibition of bile output by LPS might be mainly due to the reduction of bile acid independent component.

It was concluded that LPS inhibits hepatic bile output and it might play a role in the pathogenesis of the cholestatic jaundice seen during gram-negarive sepsis.

Modulation of hepatotoxicity by macrophages in the liver

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Monocytes and granulocytes play a key role in host defense. However, phagocytosis by monocytes stimulates thier oxidative metabolism. The increased capacity to generate oxidative radicals could contribute to the cytotoxic activities of macrophages. In the present study, to elucidate the role of hepatic macrophages in liver injury, we investigated galactosamine (GalN; 500mg/kg) treated rats. The rats were injected with latex particles prior to 12-16 hrs subsequent to GalN treatment (L-GalN or GalN-L), to alter the function of hepatic macrophages. Furthermore, we examined the effect of superoxide dismutase (SOD) on liver injury induced by GalN or GalN-L treatment. Oxygen derived-free radical generating capacity of isolated hepatic mecrophages was measured as chemiluminescence with the stimulation of phorbol myristate acetate (PMA) or latex particils in vitro.

Comparing with normal rats, chemiluminescence of hepatic macrophages from GalN treated rats was 5-10 fold enhanced after 12 hrs follwing GalN treatment, and it continued till 60 hrs. Chemiluminescence of the cells from the L-GalN treatment rats was markedly decreased as compared with GalN rats ($p<0.01$). Comparing with GalN treated rats, lipid peroxide level in the liver tissue, GOT and GPT concentrations in serum were significantly decreased in the L-GalN rats ($p<0.01$), while those were enhanced in the GalN-L treatment ($p<0.01$). SOD supplementation protects liver injury induced by the GalN-L treatment ($p<0.01$). Histological examinations revealed that a minor hepatocyte damage was detected in the L-GalN rats in ccntrast to marked liver injury in the GalN-L rats. These results suggest that pre-treatment of latex particles suppressed free radical genarating capacity of hepatic macrophages, protects liver against hepatic injury induced

by GalN. Furthermore, an injection of latex particles after GalN treatment aggravated hapetic injury and its aggravation was protected by SOD, suggest that liver injury is modulated by oxygen derived-free radicals from hepatic macrophages.

Study on the role of endotoxin in a mouse model of acute hepatic necrosis

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This study is based on our model of experimental hepatitis produced by immunizing C57BL/6 mice with syngeneic liver antigens and complete Freund's adjuvant (CFA)[1]. Moderate mononuclear cell infiltration occurs in the liver of these hepatitis mice. When such hepatitis mice were given i.v. a single dose (25μg) of lipo-polysaccharide (LPS) derived from E. coli, 70% of these mice died within 48 hr. Liver histology showed massive necrosis of hepatocytes and intensive infiltration of inlammatory cells. Serum LDH and AST levels were markedly elevated. The same dose of LPS caused milder reactions in mice with much less infiltrate in the liver folowing 1-2 immunization with liver antigen and CFA. The role of infiltrating cells in development of liver injuries was investigated by an *in vitro* cytotoxic assay system using isolated hepatocytes as the target cells[2]. The target hepatocytes were not injured by LPS alone, but readily distroyed when LPS was added to the assay system with infiltrating cells obtained from hepatitis mouse liver. These results indicate that infiltrating cells in the liver play an important role in the acute hepatocyte necrosis induced in hepatitis mice by LPS.

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Treatment of endotoxin shock in gram-negative bacteremia

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To elucidate the significance of the removal of endotoxin (Et) in gram-negative bacteremia, 5×10^9 CFU/ml/kg of E. Coli was injected intravenously for 1 hr. into 30 puppies and they were divided into 6 groups according to the treatment modalities which started at the completion of E. Coli injection. These 6 groups included plasma cross circulation[1] (PC, n=5), plasma exchange (PE, n=5), plasma perfusion over DHP-1 charcoal (n=4), hemofiltration using polysulfone membrane (HF, n=4), sham treated (n=4) and untreated (n=7) groups. 80 ml/kg of plasma of septic puppy was replaced during 2 hrs. with fresh plasma simultaneously obtained from healthy adult dog in PC group and with fresh frozen plasma in PE group.

As the results, 4 out of 5 puppies survived in PC, 1 out of 5 puppies survived in PE, while all other puppies died within 24 hrs. Viable cell counts of E. coli in PC decreased to 2.5×10^1 CFU/ml at 3 hrs. of experiment, while they were 5.5×10^2, 1.93×10^2, 2.3×10^2, 1.3×10^3 and 8.2×10^2 CFU/ml in PE, charcoal, HF, sham and untreated groups, respectively. Et concentration decreased to 5.0×10^1 pg/ml in PC, while they were 1.37×10^2, 1.97×10^2, 2.91×10^2, 1.4×10^2 and 3.5×10^2 pg/ml, respectively. Opsonic activity decreased from 0.75 to 0.3 after E. coli injection, however it recoverd to 0.56, 0.47, 0.46 and 0.41 in HF, PC, charcoal and PE groups, respectively.

Since the removal of Et and augmentation of opsonic activity can be achieved simultaneously, plasma cross circulation is the most effective treatment modality for gram-negative bacteremia.

Reference

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Symposium-3

Pathogenesis and treatment of Crohn's disease

Moderators: Yutaka YOSHIDA and Tetsuichiro MUTO

Clinical course of Crohn's disease

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Out of 86 patients diagnosed as having Crohn's disease in our clinic between 1979 and 1987, 68 patients who had not undergone an operation at the time of diagnosis, were entered into the trail. Cummulative operative rate after the onset of Crohn's disease is 7.4%, 18.3%, 34.5%, 47.8% and 55.9% at 1yr, 3yr, 5yr, 7yr, and 10yr, respectively. Cummulative operative rate after the time of the diagnosis is 17.6%, 34.2%, 51.4%, 55.6% and 61.2% at 1yr, 3yr, 5yr, 7yr and 9yr, respectively. Eighteen out of 29 patients with small bowel disease (62%), 12 out of 29 patients with ileocolic disease (41%), and one out of 10 patients with colonic disease (10%), respectively, were surgically treated.

Quality of life was assessed every each month as follows; patients' quality of life was assessed as QL 1 when their activity of daily life, official work, school life were kept normal; QL 2 when their activity was mildly limited, but they can work more than three weeks in a month; QL 3 when their activity was moderately limited, but they can work from 2 to 3 weeks in a month; QL 4 when their activity was severely limited, and they can work less than 2 weeks in a month. The total follow-up period of 68 patients was 1987 person-month. As a result, the frequency of QL 1 was 58.5%, QL 2 14.3%, QL 3 7.0% and QL 4 20.2%, respectively. There were no significant differences in incidence of Quality of Life among anatomical patterns. The incidence of active signs of inflammation in patients in QL 1 (ESR/1hr more than 20 mm, and CRP more than 1+) was 68.7%.

Nutritional therapy for Crohn's disease from viewpoint of fat absorption

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Aim: This study was undertaken to evaluate the enteral hyperalimentation from the viewpoint of disturbance of fat absorption.

Method: Enteral hyperalimentation was performed for 14 patients of Crohn's disease. Elemental diet and low residue diets were used. Patients were divided into two groups by daily fat intake of more or less than 20g. Parameters such as % body weight, total protein, albumin, total cholesterol, bowel movement, ESR, CRP, IOIBD were compared with those between before and during nutrition. Resting energy expenditure (REE) and postprandial energy expenditure (PEE) were measured by indirect calorimetry in some patients of Crohn's disease for nutritional assessment.

Results: Patients with moderate disturbance of fat absorption continued to be diarrheal state during administration of fat rich diets more than 20g, and had less increase of total protein and albumin than low fat diets less than 20g. Similarly patients with small intestinal involvement, severe diarrhea, hypoproteinemia were not suitable for fat rich diets. In 2 patients, REE was gradually increased with improvement of illness. PEE was increased than REE, but after infusion of fat emulsion without carbohydrate, RQ tended to keton body production.

Conclusion: We must choose low fat and low residue diets for management of patients of Crohn's disease with fat malabsorption or severe diarrhea. In case of low fat diets, we must supply essential fatty acid by fat emulsion with administration of carbohydrate.

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Hypothetical working mechanism on total elemental enteral hyperalimentation in Crohn's disease

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Total elemental enteral hyperalimentation (TEEH) has been accepted as a primary therapy of Crohn's disease (CD). Defining its working mechanism is quite important to clarify a possible pathogenesis of CD. We proposed the following hypothetical working mechanism on TEEH: namely, 1) repletion of protein-calorie malnutrition (PCM), 2) elimination of luminal antigens ((a) alternation of enteric bacterial flora, (b) elimination of dietary antigens) and 3) keeping bowel rest.

Aim: An aim of this study was to investigate a feasibility of the hypothetical working mechanism.

Subjects and methods: 1) PCM: 26 patients with CD were treated with TEEH and nutritional assessments were performed before and after the treatment, and their results were compared. 2) Fecal flora: In 8 patients with CD, quantitative aerobic and anaerobic cultures of feces were performed before and during the TEEH and cultured species were expressed by %, and their changes were compared. 3) Dietary antigen: Patients with inactive CD were followed with or without sliding-scale based cyclic home elemental enteral alimentation (HEEH) which consists of nocturnal ED + daytime low residue foods (the amount of ED was increased and low residue foods was decreased when flare-up occurred). Their remission rates and non-hospitalization rates were compared. 4) Bowel rest: Entire colonic motility study was performed as previously reported. Effects of ED, defined formula diet (DFD), amino acids and fat on the colonic motility were studied and their motility indicies (M.I.) were compared.

Results: 1) Repletion of PCM: In all cases, repletion of PCM was obtained (BW 6.64±4.0 kg$^{\uparrow}$ T-protein 1.31±0.81$^{\uparrow}$, Albumin 1.18±0.63 gldl$^{\uparrow}$, TSF 3.3±3.6 mm$^{\uparrow}$, AMC 1.26±0.94 cm$^{\uparrow}$. 2) Alternation of the fecal flora: Increased bacteroid fragilis group, decreased bifidobacterium adlescentis and increased streptococcus fecalis were the typical pattern in patients with TEEH. 3) Dietary antigens: HEEH prevented flare-up CD and even after flare-up, remission was re-obtained in majority of cases by decreasing oral intake of low residue foods and increasing amount of ED. 4) Bowel rest: ED kept more bowel rest than DFD, Fat was the major nutrient to accelerate the colonic motility.

Conclusions: The above results support our hypothesis on working mechanism of TEEH in CD which includes 1) repletion of PCM, 2) elimination of luminal antigens (alternation of enteric bacterial flora, elimination of dietary antigens) and 3) keeping better bowel rest.

Assessment of the therapeutic value of nutritional therapy in the treatment of Crohn's disease

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We assessed the value of primary nutritional therapy in the treatment of Crohn's disease in several conditions. Total parenteral nutrition (TPN) was done in 45 patients (67 times), elemental diet (ED) in 25 (32 times), and low residue diet (LRD) in 12 (12 times). As an initial therapy to the patients without previous treatment TPN was performed in 13 patients and ED in 15.

Results and Conclusions

1. The rates of complete remission by nutritional therapy were lower in patients with longer duration of symptoms or in patients with previous operation.
2. TPN, ED or LRD were very useful in the

treatment of patients with Crohn's disease without previous therapy.
3. In patients with Crohn's disease whose CDAI was more than 100 X-ray examination showed active lesions in the small or large bowels. Therefore, complete remission should be determined as having CDAI less than 100.
4. The effect of TPN and ED was similar in treating patients with Crohn's disease without previous therapy.
5. The rates of complete remission by TPN or ED were lower in patients with intestinal or extra-intestinal complications.
6. It is concluded that the initial nutritional therapy successful in inducing the complete remission is favorable prognostic factor.

Monocyte dysfunction and 6-mercaptopurine (6-MP) therapy in Crohn's disease

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Although the pathogenesis of Crohn's disease (CD) is uncertain, there is accumulating evidence that monocyte-macrophage may have some role in the formation of intestinal lesions in this disease. In the present study, monocyte functions were investigated by several methods and the therapeutic effect of 6-mercaptopurine (6-MP) was analyzed in 46 patients with CD. The production of oxygen-derived free radicals of peripheral blood monocytes was examined using chemiluminescence assay. It was remarkably increased in the patients in comparison with in healthy controls. Surface markers expressed on peripheral blood or intestinal monocyte-macrophage were studied using monoclonal antibodies. Flow cytometry analysis revealed the presence of both transferrin receptor positive and LeuM3 positive monocytes in the patients and immunohistochemical studies showed the numerous LeuM3 positive cells with transferrin receptor in the intestinal lesions of the patients. These data indicate the presence of activated monocytes in CD. We have reported that the immunosuppressive factor was present in the serum of the patients. The fractionization of culture supernatants of mononuclear cells revealed that the immunosuppressive factor found in the serum of CD patients was produced by peripheral blood monocytes. The effect of 6-MP treatment on these monocyte functions and clinical state was further examined. 6-MP treatment was effective in closing or improving the fistula as well as in reducing the CD activity index (CDAI). Immunosuppressive activity of the serum and the production of oxygen-derived free radicals were both reduced in patients treated with 6-MP. It is suggested that 6-MP is effective in CD patients who were resistant to the conventional therapy by improving the monocyte dysfunction found in these patients.

Essential fatty acids deficiency in Crohn's disease and treatment of Crohn's disease with cyclosporin A

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The cause of essential fatty acid deficiency in Crohn's disease was investigated by measuring bile acid analysis, fecal fat excretion, food intake and energy expenditure. Thirty-one cases of ileitis and ileocolitis of Crohn's disease were studied. Their serum linoleic acid concentration was decreased in parallel to severity of Crohn's disease and improved after the treatment in majority of cases. Serum linoleic acid concentration was also low in the most of mild and moderate cases.

Bile acid concentration, fecal fat exretion were not directly related to serum linoleic acid concentration and energy expenditure was not also related to serum linoleic acid concentration. Serum linoleic acid concentration was closely related to oral fat intake.

Cyclosporin A was given to seven active

Crohn's disease patients for 16 weeks or longer. Initial dose of cyclosporin A was 8 mg/kg/day and subsequent dose was adjusted to maintain plasma concentration approximately 200 ng/ml. Mean CDAI before treatment was 194 ± 57. It was gradually lowered and was the lowest at 12 weeks (139±34, $p<0.05$) and one enterocutaneous fistula was closed. But white blood cell, hemoglobin and alpha two globulin were not significantly improved. Cyclosporin A would be indicated when steroid, sulfasalazine and/or azathioprin were not effective or tolerated.

The long-term outcome of surgical treatment for Crohn's disease

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The long-term outcome of Crohn's disease was reviewed in 35 patients who were treated surgically at Tohoku University Hospital from 1961 to 1986. They were 24 males and 11 females, and their total follow-up period was 10.1±5.7 years and postoperative period after initial operation was 7.6±5.5 years.

The cumulative risk of reoperation was about 30% at 5 years and 50% at 10 years after initial operation. The cumulative risk of reoperation after the second operation was higher than that after initial operation, that is, 57% at 5 years after the second operation. The cumulative risk of recurrence after "curative" resection was very high, i.e., 69% at 6 years after operation, however the cumulative risk of reoperation was much lower than the recurrence rate, i.e., 30% at 6 years after operation. The prognosis after "curative" resection seemed to be almost similar to the prognosis after "non-curative" resection. Concerning the length of lesion and the extent of the resected disease-free margin, they were significantly greater in the patients with recurrence than in those without recurrence after "curative" resection. Therefore the larger the extent of disease, the sooner the recurrence was thought to develop.

In conclusion, the surgical treatment in Crohn's disease was always accompanied by the risk of recurrence and reoperation, so the regular follow-up and investigation are very important. And it was illustrated that longer disease-free margin couldn't improve the surgical results.

Panel discussion-1

Medical and surgical alternatives in the treatment of peptic ulcer

Moderators: Saburo OHSHIBA and Hisaaki SHIMAZU

Treatments of peptic ulcer –Pros and Cons in conservative and surgical treatments–

Teruaki AOKI
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H_2-receptor antagonists (H_2-RA) have obtained great reputations that they could wipe out all ulcer-symptoms quickly and could make them healed in a very short period. On the other hand, however, it is becoming apparent that, to prevent ulcer recurrence, it is mandatory to continue medications almost permanently.

Nation-wide survey, performed by us, revealed that marked reduction in total number of peptic ulcer surgery, but no or very little reduction in number of surgery for bleeding, perforated or stenotic ulcer patients on emergency bases.

Almost no improvement has been obtained in peptic ulcer surgery in terms of recurrent rates of anastomotic ulcer and motality rates.

This could be explained by the limited occasions to have training for ulcer surgery on elective bases.

It is clear that the more physiological and function-preserving ulcer surgery must be widely used in Japan and for the purpose, not only surgeons but also gastroenterologists must recognize that the surgical indications for patients with noncurable peptic ulcer disease, must be considered at more appropriate timing.

Operative indications for surgical treatment of peptic ulcer, including AGML, before and after introduction of H_2 blockers

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The purpose of this study was to review the records of patients undergoing surgery for chronic peptic ulcer (CPU), including AGML, before and after the advent of H_2 blockers, to determine if patient characteristics, operative indications, and surgical management, have changed.

Patients: Patients consisted of 840 CPU and 25 AGML cases between the years 1967 and 1978 (Group 1), and 192 CPU and 44 AGML cases between 1979 and 1986 (Group 2).

Indications for surgery in CPU: The average number of patients per year operated upon was 70 cases in Group 1 and 24 cases in Group 2 ($p<0.001$). The frequency of emergency surgery was 22.3 per cent in Group 1 and 38.6 per cent in Group 2, and the relative increase in Group 2 was particularly with cases of hemorrhage and stenosis. The role of surgical treatment for gastroduodenal hemorrhage has reduced substantially, with recent advances in the use of the endoscope for hemostatic purposes, coupled with the availability of effective H_2 blockers and secretin preparation.

Surgical management: From 1967 to 1976 we performed operative procedures (SV + antrectomy, SV + pyloroplasty, and antrectomy alone) based on medical vagotomy, but thereafter have performed SV + antrectomy for all CPU cases except the gastric ulcers of normosecretors. The mortality rate of AGML patients who received conservative treatment was 83.3 per cent in Group 1, and 21.4 per cent

in Group 2. The frequency of emergency surgery for AGML decreased significantly from 55.6 per cent (Group 1) to 4.6 per cent (Group 2). We performed near total gastrectomies with SV or TV for AGML cases.

Indication of surgical treatment for peptic ulcers

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The purpose of surgical treatment of peptic ulcer is not only to heal the ulcer and prevent the recurrence by adequate reduction of acid secretion but also to preserve gastric function as much as possible. In our department the selective operations have been performed for total 1175 patients since 1961, such as gastrectomy, gastrectomy with vagotomy, or vagotomy according to the characteristic of each patient. The Visick grading of each operation showed good results (Visick I and II) in 90 to 98% of the patients.

However, the numbers of the operations for intractable ulcers have been markedly decreased recently year by year. On the other hand, the incidences of the perforation and the bleeding have not been decreased. Perhaps medical treatment could hardly prevent them, because 48% of the patients had no history of ulcer, and the others developed unexpectedly. And we lost 6 (3.1%) out of 195 patients with perforated gastric or duodenal ulcer we investigated during recent 5 years in Niigata city, Japan.

Analyzing the data, patients with perforated ulcer will undergo any operation safely, if they have no severe preoperative complications such as hypotention, cerebral, chronic inflammatory or renal disease, and receive operation within 24 hours from perforation.

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Present status of surgical treatment of peptic ulcers

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The author reviewed the cases of peptic ulcers who were surgically treated at the First Department of Surgery of Kobe University Hospital over the past 10 years. Analysis of these cases, dividing the ten years into two (first and latter) terms, provided the following findings. (1) In the latter term, surgically treated ulcer cases decreased. (2) The percentage of hemorrhagic ulcer cases who underwent emergency surgery became higher in the latter term; at the same time, the fatality of hemorrhagic ulcers increased from 26% in the first term to 40% in the latter. (3) During the ten years, 8 cases of perforated ulcers were surgically treated, and 50% of them died. Analysis of the relationship of death with background variables disclosed that the fatality was higher in perforated ulcer cases carrying additional disease(s), elderly patients with perforated ulcers and ulcer cases carrying a large perforation (over 2 cm in diameter). (4) The number of surgically treated cases of stenosal ulcers was 7 in the first term. It decreased to 3 in the latter term because of an increase in the cases who rapidly responded to antiulcer drug therapy under fasting and TPN management.

Complication and recurrence of gastric ulcer

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1. Complication

From long-term follow-up study (for 2,511 cases and average 5 years) of healed gastric

ulcer, ulcer death were encountered in 10 cases, in which 8 were of hemorrhage and 2 were of perforation. Besides ulcer death, 14 of cancer, 11 of heart disease and brain vascural lesions were encountered. Therefore, bleeding from recurrent ulcer is most frequent and most serious complication of recurrent gastric ulcer. Analysis of 1066 cases which were operated on during past 25 years, revealed remarkable decreasing in its number since 1981, when H_2 blocker was applied to clinical use including experimental use in our hospital. Operated cases with hemorrhage decreased extremely since 1984, when endoscopic hemostasis was frequently applied.

2. Recurrent ratio of gastric ulcer

As being already reported, recurrent ratio of gastric ulcer was about 10% a year. On the other hand, recurrent ratio excepting wash-out method (wash-out red scar or 6 months after healing) reached to 11.4% in 6 months and 24.8% in 12 months. Judging from the data which suggest maintenance therapy is extremely effective for recurrent during 6 months after healing, we conclude maintenance therapy is necessary during red scar stage or for 6 to 12 months after healing.

3. Intractable gastric ulcer

In intractable ulcer (more than 6 month resist for medical treatment), acid secretion was less responded with H_2 blocker. Therefore, combination therapy should be necessary for treatment of intractable ulcer cases.

The limits in therapy by internal medicine for peptic ulcer disease

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The curative rate of the gastric ulcer by the application of histamine H_2 receptor antagonist (H_2 blocker) indicates a significant high ratio 8 weeks after the application as compared with the treatment with the conventional mixture of the antiacid and the anticholinergic drugs. However, there is no significant difference 12 weeks later. H_2 blocker is also effective against the ulcer in the gastric body with low acid secretion, but again there is no difference 8 and 12 weeks later in the curative ratio as compared with the treatment with the antiacid.

The clinical background of the H_2 blocker resistant ulcer is similar to that of the usual protracted healing ulcers. The finding with the endoscopic ultrasonography suggests the deep ulcer with thick fibrous tissue in the bottom of the ulcer. Therefore, many of the ulcers which are difficult to be cured with the conventional antiulcer drugs may also present the protracted healing even with the H_2 blocker. The another problem in the treatment by H_2 blocker is the high incidence of recurrence after stopping the dose of H_2 blocker. Furthermore, the recurrence may often happen even during the period of maintenance therapy with H_2 blocker, and most of the cases are without the symptoms. There exists the limit of the therapy by drugs, where the natural history of the peptic ulcer disease cannot be changed even by the H_2 blocker application. However, after the introduction of H_2 blocker, the number of surgical operation decreases in the cases of gastric and duodenal ulcers. Specially, the number is decreasing in the cases where the surgery has been performed due to the reason in the difficulty in cure and the repeated recurrence of ulcer. This tendency is mainly because it may become easier by the introduction of H_2 blocker to control the subjective symptoms of the patient with ulcer. There is not much difference in the emergency operation incidence of the bleeding cases of the gastric ulcer where the hemostasis is difficult and the perforation cases of the duodenal ulcer.

Medical treatment of gastric ulcer disease

Masakazu MARUYAMA
Department of Internal Medicine, Cancer Institute Hospital

Some problems on the medical treatment of gastric ulcer disease were studied, based on the

computer-processed data of 1,034 patients in whom follow-up examinations by x-ray and endoscopy had been performed for more than 3 years since 1982 at the Cancer Institute Hospital, Tokyo, Japan.

The patients with gastric ulcer disease were divided into 3 groups, including 109 patients (10.5%) without recurrence in all examinations, 876 patients with recurrence of more than one time, and 49 patients without healing in all examinations.

Comparison of the medication rate in two groups of the patients without recurrence and without healing revealed that continuation of the medication caused no influence on the recurrence or healing of ulcer. However, comparison of H_2-antagonists and the other no specific anti-ulcer therapy in the two groups of the patients disclosed that the recurrence or non-healing rate was significantly high in the patients treated with H_2-antagonists.

The time required for ulcer healing is shortened by the use of H_2-antagonists, in addition to early disappearance of epigastric pain. However, such characteristics of H_2-antagonists may cause discontinuation of the medication for a relatively long time, which is closely related to the recurrence or non-healing of ulcer. It was suggested that H_2-antagonists are not necessarily used for gastric ulcer disease in a long-term prospect.

Evaluation of medical treatment for peptic ulcer disease

Katsunori SAIGENJI
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Most cases of peptic ulcer disease were treated medically, especially, with H_2-receptor antagonist today. I reported the efficacy of medical treatment and surgical indication of peptic ulcer diseases.

Six weeks healing rate was 87.1% (149 cases) in duodenal ulcer, and 8 weeks healing rate was 76.4% (237 cases) in gastric ulcer respectively. In recurrent cases 79.2% of duodenal ulcer were healed at 6 weeks, and 74.8% cases of gastric ulcer were healed at 8 weeks. So H_2-receptor antagonist was equally effective to recurrent ulcer. But, once healed ulcers were easily relapsed, and 2 years remission rate were 48.3% in gastric ulcers and 61.7% in duodenal ulcers.

Since 1982, cimetidine was on the market, surgical cases were markedly decreased. During 1977 to 1981, 289 cases of peptic ulcer were operated, and 168 cases were operated subsequent 5 years. Especially, surgical cases operated because of intractability were markedly decreased, and emergent operated ratio increased relatively.

Panel discussion-2

Update in diagnosis and treatment of severe acute pancreatitis

Moderators: Yoichi SAITO and Satoshi NAKANO

Clinical aspects and prognostic signs of severe acute pancreatitis

Yuji HORIGUCHI
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In 1985, we reported diagnostic criteria for severe pancreatitis based on assessment of definite cases by laparotomy. Recently new criteria, that are almost the same as ours except for imaging findings, were proposed by Japanese Ministry of Health and Welfare. In this study, therefore, I analysed recent cases of acute pancreatitis in the past 7 years after advent of CT and ultrasound.

Subjects

According to the criteria by the Ministry of Health and Welfare, 266 cases were divided into 3 groups, i.e. severe form (43 cases), moderate form (44 cases), and mild form (179 cases). There was no difference in mean age and etiology among fatal, severe and moderate cases.

Results

On admission, hypotension, renal failure, and dyspnea were observed in 65, 49, and 60% out of 43 patients with severe form in contrast with 2, 14, and 9% of moderate form, respectively. The grade of peritoneal sign was significantly greater in severe form. Laboratory data on admission indicated that Ht (≧50%), BUN (≧30mg/dl), FBS (≧200mg/dl), LDH (≧700U/l), calcium (≦7.5mg/dl), PaO_2 (≦60mmHg), and base excess (≦−5mEq/l) were efficient parameters for judgement of severity. In addition, hypoproteinemia and thronbocytopenia with elevation of FDP were seemed to be poor-prognostic findings. CT findings such as ill-defined thickness of the pancreas, uneven internal texture, fluid collection, and edema of pararenal space were also valuable for predicting the severity. The mortality rate was 6.7% (41.8% of severe form). The main cause of death was cardiovascular failure (6 cases), renal failure (4 cases) or respiratory failure (6 cases).

Conclusion

Interdisciplinary judgement of severity in combination with physical, laboratory and morphological examinations might facilitate our appropriate managements to acute pancreatitis.

Severity of acute pancreatitis and its diagnosis by US and CT

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With the advance in US and CT, diagnostic imaging has become possible for acute pancreatitis. In this session, we discussed the diagnosis of this disease and determination of its prognosis by US and CT.

Subjects

We experienced 84 cases of acute pancreatitis. Of these patients, 48 (17 mild, 21 moderate and 10 severe cases) underwent diagnostic imaging by US and CT.

Method

The diagnostic imaging were compared with the severity of the disease. CT score, which were calculated by regarding each of 22 items of CT findings as one point.

Results

1. US was useful in differentiating between mild and severe cases, but not between moderate and severe cases.
2. CT was valuable in differentiating among mild, moderate and severe cases. Quantitative diagnosis with CT scores was also

useful for differential diagnosis.

Conclusion

A relationship was recognized between the location of fluid retention detected by diagnostic imaging and the severity of acute pancreatitis, and this relation was very useful in planning treatment.

Surgical indication and its timing in gallstone pancreatitis

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The operative result of 98 patients with gallstone pancreatitis who had severe abdominal pain and concomitant elevation of serum amylase, transaminase and T. bilirubin and gallstone in the distended bile duct and/or gallbladder was reported. Sixty-five patients (66.3%) underwent emergency operation during an episode of pain mainly because of the severity of the symptoms. At laparotomy, an impacted bile duct stone at the ampulla was identified in 30 (46.2%) of 65 patients, acute suppurative cholangitis (ASC: pus in the bile duct) in 23 (35.4%) and severe acute pancreatitis (hemorrhagic and necrotic pancreatitis) in 14 (21.5%). Seven patients (10.8%) died. Early postoperative death occurred in 3 (2 due to ASC and 1, severe acute pancreatitis). Three patients with severe acute pancreatitis died late postoperatively due to MOF related to intraabdominal abscess. The remaining 1 patient died of unrelated disease.

In summary, when the diagnosis of gallstone pancreatitis is made and the severity of the symptoms persists, urgent operation is mandatory to disimpact the stone at the ampulla, preventing from its progression to ASC and/or severe acute pancreatitis.

The role of plasmapheresis in the treatment of acute pancreatitis

Masahiro YAMAMOTO

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The therapeutic problems and countermeasures of acute pancreatitis were discussed by analysing data on 59 severe cases according to the criteria classified by the Research Committee of Intractable Diseases of the Pancreas supported by Japanese Ministry of Health and Welfare, of 218 patients we experienced recently. Of these, 36 patients had the early complications such as shock, renal failure, respiratory insufficiency, and so on. In 25 cases in which surgical treatment was applied when the general condition worsens or fails to improve despite conventional conservative therapy, the mortality showed 27.3%, and the preoperative existence of important organ involvement was related to the cause of death from postoperative multiple organ failure. In the cases in which plasmapheresis, a new therapeutic trial was performed for the treatment of associated multiple organ involvement, the improvement in early mortality were observed. In an experimental examination made on the therapeutic model for hemorrhagic necrotizing pancreatitis in dogs, the importance of removal of enzymes or toxic substances from inside the body and replacement of fresh plasma by means of plasmapheresis was demonstrated on preventing the impairment of other organs and preserving the organic protective mechanism. Based upon these clinical studies and the experimental results, it has been concluded that in the case the condition is aggravated without obtaining desirable effects from conservative treatment, it is important to depend upon the performance of surgical treatment safely, cutting off the vicious circle in pancreatitis and improving the organ involvement by means of the plasmapheresis besides the other intensive management.

Mechanisms for aggravation and development of multiple organ failure in severe acute pancreatitis

Michio OGAWA
Second Department of Surgery, Osaka University Medical School

Two possible mechanisms for aggravation and development of multiple organ failure in severe acute pancreatitis are stressed here: 1) Endotoxemia in severe acute pancreatitis which damages cell surface phospholipids, and 2) activation of neutrophil and release of neutral proteases such as neutrophil elastase and superoxide. We demonstrated *in vitro* activation of neutrophils by endotoxin and cytokines. The destruction and dysfunction of remote organs in severe pancreatitis may be explained by these two mechanisms which has so far eluded investigaters.

Medical treatment for acute pancreatitis

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This time, we investigated the efficacy of the protease inhibitor (PI), antibioticus and H_2-receptor antagonist for medical treatment in acute pancreatitis. In basic study, the pancreatic enzyme levels, especially, trypsin like activity (TLA)[1] were decreased strongly in serum, but TLA in ascites not significantly suppressed by intravenous injection (IV) of the PI in the acute experimental pancreatitis dogs. On the other hand, TLA in ascites dropped rapidly and strongly by intraperitoneal bolus injection (IP) of the PI[2,3] The PI was excreted rapidly from the serum. On the contrary, TLA went up again after disappearance of that drug.[4] With a new treatment, the continuous intravenous injection (CIV) of the PI, the pancreatic enzyme levels decreased significantly with time in the serum. In CIV, the decrease of ascites TLA was more significant than that in IV group but it took longer time until TLA drops when compared with that of IP group. The combination therapy of CIV and IP was the best in our clinical trial which was performed on the basis of our experiments. Antibioticus that was injected intravenously was detected in the pancreatic juice and in pancreatic tissue, which content was 10 times higher than in the pancreatic juice. H_2-receptor antagonist that admitted for 2 hours intravenously decreased pancreatic exocrine secretion significantly. We concluded that CIV was better than IV, moreover, the combination therapy of CIV with IP was the best for the treatment of acute pancreatitis. H_2-receptor antagonist and antibioticus were useful treatment for acute pancreatitis.

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Panel discussion-3

Hepatic regeneration and its modulation with therapeutic measures

Moderators: Michio MITO and Shunichi SATO

Clinical evaluation of liver regeneration in fulminant hepatitis

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In this paper, time course of changes in "integrated CT number" (ICTN) in combination with plasma cAMP response to exogenous glucagon ($\Delta cAMP_{15}$) was particularly assessed to evaluate the regenerative liver growth in fulminant hepatitis (FH) and its relating disorders. ICTN (liter × Hounsfield unit), representing the residual liver mass, was calculated by integrating area times CT number of each liver slice with a use of Lagrange's equation, since heterogeneous low density areas on liver CT imaging were not infrequently observed in some patients with FH, especially subacute clinical type.

ICTN was found to be significantly decreased in the order of subacute hepatitis (SAH; 36.3±10.5), non-fatal (38.5±6.5) and fatal FH (14.1±2.7), as compared with in normal subjects (56.6±10.1), acute hepatitis (AH; 59.8±12.9) and its severe form (AH_s; 56.2±18.7). With respect to clinical course, ICTN in AH_s and non-fatal FH were found to be transiently overshoot from the normal range (a peak around 10-20 days). On the other hand, in patients with SAH, ICTN tended to recover toward normal at the extremely slower rate (under the normal range even after 3-4 months) than in cases of survived FH, strongly suggesting "impaired liver regeneration". Of particular interest was the fact that a significant positive correlation ($r=0.988$, $p<0.001$) between ICTN and $\Delta cAMP_{15}$ was observed only in acute type, but not in subacute type of FH.

From these results, it is concluded that regenerative process of the liver is heterogeneous according to the clinical type of FH, and ICTN is clinically important for evaluating the prognosis of FH prior to several heroic medical interventions recently introduced.

Liver regeneration and its stimulation in fulminant hepatitis

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Most patients of fulminant hepatitis with prothrombin time (PT) less than 10% of normal showed serum AFP levels below 10 ng/ml, and died irrespective of therapies. In case of PT greater than 10%, they increased above 10 ng/ml after 3 days from disease onset. In non-survivors, however, they gradually decreased and PT did not exceed 50% in contrast to survivors who showed reverse changes. Liver regeneration is less likely to occur in fulminant hepatitis with a certain extent of hepatocellular dysfunction.

Glucagon and insulin (GI) additively enhanced hepatic content of putrescine necessary for regeneration in post-hepatectomized rat liver. Infusion of GI for one week significantly increased the number of patients with severe type of acute viral hepatitis in whom serum AFP levels were gradually elevated during treatment but dropped after its discontinuation, compared with the placebo group. GI may be indicated for stimulation of liver regeneration in fulminant hepatitis with PT greater than 10%.

In rats after a dose of hepatotoxin, exchange transfusion prolonged survival time with improved PT and enhanced hepatic protein

synthesis, and produced better histological grade of recovery from liver injury in survivors. A similar result was also seen after plasma supplementation. Both treatments did not affect hepatic DNA synthesis after injury and hepatic putrescine content after partial hepatectomy. Plasma exchange seems beneficial for recovery from liver injury mainly through plasma supplementation.

Clinical study on liver regeneration after major hepatectomy

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Regeneration of hepatic volume and function after major hepatectomy was studied comparatively in 30 patients. Morphologic feature of the remnant liver revealed to be almost normal in 10, mild to severe fibrosis in 12 and definite cirrhosis in 8. The volume of regenerating liver was calculated by computed tomography (CT), and the function was measured by maximum removal rate (Rmax) and 30 min retention rate after 5 mg/kg administration ($_5R_{30}$) of indocyanine green (ICG) and hepaplastin test (HPT).

The rate of volume regeneration one month after hepatectomy satisfactorily revealed 92% in normal liver patients, 79% in fibrotic liver and 83% in cirrhotic liver. While the rate of functional regeneration measured by ICG Rmax showed only 52%, 49% and 46% respectively. The rate in ICG $_5R_{30}$ revealed much closer correlation with the volume change but did not exceed the rate observed by HPT.

Compared with the volume regeneration, hepatic functional recovery estimated by ICG tolerance showed marked delay. The discrepancy indicated its role on the treatment after major hepatectomy.

Significance of glucagon and insulin in therapy of fulminant hepatitis

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A report[1] that an appropriate dose of glucagon and insulin given simultaneously was capable of restoring DNA synthesis to normal in the partially hepatectomized, eviscerated rat, even though the hepatic blood supply was reduced to a functional volume provided only by the hepatic artery. Based upon those evidences, study to assess the usefulness of those hormones in the therapy of fulminant hepatitis has been performed, resulting in an improvement of survival rate and consciousness[2].

The survival rate was higher in the patients treated with glucagon and insulin (6/14, 42%) and with the infusion of these hormones plus plasmapheresis (6/19, 32%), as compared with that obtained through a national survey in Japan[3].

Concerning the improved survival rate in the patients infused glucagon and insulin simultaneously, our study used the animals carrying severe liver injury showed clearly that simultaneous administration of both hormones enhanced regenerating capacity of the liver, because the factors involved in the process of cell cycle from Go to S, such as cAMP, ODC, thymidine kinase increased after treatment with hormones.

Furthermore, an increase of hepatic blood flow due to both hormones administered in the same manner was observed not only in the normal rats, but also in those injected a very high dose of galactosamine known as a potent hepatotoxin. In this panel discussion, possible application of EGF in combination with glucagon and insulin therapy was also argued.

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Effects of prostaglandin E_1 and glucagon-insulin on hepatic regeneration in liver injury

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D-galactosamine damaged rats were infused with prostaglandin E_1 (PGE_1) through a peripheral vein for 40 min before and after partial hepatectomy. DNA synthesis following 68% partial hepatectomy was severely inhibited by the pretreatment of D-galactosamine. PGE_1 infusion enhanced DNA synthesis inhibited by D-gal 600mg/kg significantly ($p<0.01$). 20 min and 12 hr after PGE_1 infusion cyclic AMP levels of liver tissue was increased as compared with saline infusion in D-gal damaged rats ($p<0.05$). Also 20 min and 3 hr after partial hepatectomy ATP levels of liver tissue was enhanced in PGE_1 treated group ($p<0.05$).

Secondly, rats were damaged by partial liver ischemia. PGE_1 derivative remarkably suppressed the increase of free lysosomal enzyme activities of liver tissue, measured of cathepsin-D, -glucuronidase, acid-phosphatase. As well the increase of serum lysosomal enzyme activities after partial hepatic ischemia was prohibited by PGE_1 derivative. These results suggest that PGE_1 enhance DNA synthesis of injured liver after partial hepatectomy by the mechanism which PGE_1 stimulate cyclic AMP production and increase ATP level in hepatic tissue and which PGE_1 also has the effect of stabilizer for lysosomal membrane.

Clinically 20 cirrhotics with hepatocellular carcinoma were treated by PGE_1 and glucagon-insulin after hepatectomy and other 25 patients were hepatectomized without these therapy as control. Surgical mortality for hepatic failure was 15% in PGE_1 and glucagon-insulin group, which was less than 28% in control group, but not significant.

Preoperative evaluation of hepatectomy and effect of nutritional management on liver regeneration

Takashi HIGASHIGUCHI
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On hepatocellular carcinoma associated with liver cirrhosis, there is not a few cases whose hepatic resection is required beyond the functional limit in order to obtain the therapeutic radicality. The purpose of the present study is to evaluate a possibility of extended hepatic resection resulted from a nutritional management, by estimating preoperatively a regenerative capacity of the liver, using 220 patients treated in our department.

1. Preoperative evaluation of hepatectomy and regenerative capacity:

Being paid attention to a discrepancy between morphological liver regeneration and functional recovery after hepatectomy, ICGRmax per unit liver volume was measured at residual liver before surgery. When it was over 0.8, liver regeneration was satisfactory, whereas when it was below 0.5, liver regeneration was poor, so that the level between 0.8 and 0.5 was regarded as the critical.

2. Effect of nutritional management on liver regeneration:

Even in the cases of the critical level, liver regeneration was satisfactory, if nutritional statement could be maintained well before and after surgery, such as, if Prognostic Nutritional Index for Surgery (PNI-S = $-0.147 \times$ ratio of weight loss + $0.046 \times$ weight for height + $0.010 \times$ ratio of triceps skin fold thickness + $0.051 \times$ normotest) could be improved over 10 preoperatively. Furthermore, even if the preoperative PNI-S was 5~10, liver regeneration was well when over 40 kcal/kg/day of glucose and Fischer's solution were administered. In conclusion, it is very important to evaluate a regenerative capacity on an extended hepatectomy, and nutritional management may accelerate liver regeneration.

Merits and demerits of the drugs which influence the immune system in liver regeneration

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In the previous papers we reported that the immune system of mice is activated during liver regeneration following partial hepatectomy and that the activated lymphocytes suppresses several immunological responses. Furthermore, we reported that the inductive activity of autoreactive cytotoxic lymphocytes decreased temporarily after hepatectomy[3] and the activated immune competent cells modulate the regenerating process of liver in mice[4]. These results suggest that the processes of liver regeneration may be related closely with the immune system of the organism.

Therefore, we designed the experiments to clarify whether the regeneration of liver was modified by the immune modulation using some drugs (ciclosporin, glycyrryizin, prostaglandin inhibitor, H_2-antagoinist). Additional study was, furthermore, carried out to determine if the alterlation of the immune system shown in the experiments are reflected in the clinical situation.

1) Ciclosporin and glycyrryizin increased the regeneration of liver following partial hepatectomy with suppression of the immune system.
2) Prostaglandin inhibitor and H_2-antagonist slightly decreased the regeneration of liver following partial hepatectomy with the inhibition of the suppression of the immune system.

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