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Chairman: Shuji HASHIMOTO, M.D.

Symposium-3

The problems in diagnosis of pancreatic cancer

Moderators: Yoichi SAITOH and Tatsuji HOMMA

The role of ERCP, EUS, and POPS in the diagnosis of cancer of the pancreas

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The diagnosis of cancer of the pancreas has been advanced according to the progress of imaging diagnostic methods; US, CT, ERCP, and angiography. However, there remains some problems to be resolved i.e. the early diagnosis and the differential diagnosis between cancer and pancreatitis. In order to clear these problems, endoscopic ultrasonography (EUS) and peroral pancreatoscopy (POPS) have been performed in our institution for seven years.

We have investigated the role of ERCP, EUS, and POPS in the diagnosis of cancer of the pancreas. ERCP was the best accurate diagnostic procedure among imaging diagnostic methods in this disease. However, abnormal findings of the pancreatic duct system demonstrated by ERCP, especially single stenosis of the main pancreatic duct was needed the differential diagnosis between cancer and localized pancreatitis. EUS is also appreciated as a further examination of cancer of the pancreas, because tumor and dilated pancreatic duct were demonstrated by this method in cases of pancreatic cancer, even small cancer of less than 2 cm. On the other hand, POPS showed an irregular protrusion in cases of pancreatic cancer and a smooth stenosis without redness in cases of chronic pancreatitis. Therefore POPS was very useful in the differential diagnosis between cancer and localized pancreatitis.

Now, in order to get information about the diagnosis and the spreading of cancer of periampulla, we have started on a new trial of EUS-guided ERP, combining both advantages of ERCP and EUS.

Disgnosis of pancreatic cancer—with special reference to so-called mucin producing tumor—

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The early diagnosis of pancreatic cancer is still difficult. Out of 212 pancreatic cancers, 53 (25%) were treated with curative surgery, and 159 (75%) were non-curative. Of 53 resected tumor, T_1 or T_2 type tumor (less than 2.0cm or 2-4 cm in diameter) were only 8 cases (15%). The T_1 tumors disclosed the obstruction of the main pancreatic duct or the stenosis of Wirsung's duct. All cases with diffuse dilatation of the main pancreatic duct showed the tumor larger than 4.0cm in diameter. The patients with non-curative pancreatic cancer died within 2 years after surgery. Of the 53 patients treated curatively, only 2 (5%) have survived longer than 5 years. So-called mucin producing pancreatic tumor is characterized clinically by following findings of duodenofiberscopy and

ERCP. 1) Swelling Vater papilla and outflow of mucin-like substance from the dilated orifice. 2) Diffuse dilatation of the main pancreatic duct. 3) The prognosis of the patient is relatively good. As for 12 cases clinically diagnosed as mucin producing pancreatic cancer, 11 of which showed the diffuse dilatation of main pancreatic duct or branches of the uncus, 7 dilatation of the orifice of Vater papilla and 9 revealed outflow of mucin.

The final histological diagnoses were 5 pancreatic carcinoma, 2 pancreatic adenoma and 1 intrahepatic mucinous cholangiocarcinoma. The remaining 4 cases have been followed up without surgical treatment. The histological findings revealed the clear adenocarcinoma, or hyperplastic lesions or benign adenomatous lesions. The mixed findings of these were seen even in the same specimen. Three of 5 patients, who were treated surgically, have survived longer than 3 years. Of 5 non-resected patients, 1 died after mucinous pancreatic adenocarcinoma, and the others have survived excellently with the longest period of 3 years and 10 months.

It may be concluded that so-called mucin producing pancreatic tumor can be diagnosed easily with duodenofiberscopy and ERCP, and the prognosis of them is considerd as relatively good. The histopathological classification of the mucinous pancreatic tumor, including benign tumor, remains to be established.

Papillary-cystic neoplasm of the pancreas: Calcifying-inverted variant detected by plain X-rays

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We encountered four tumors showing histologically, histochemically, and ultrastructurally characteristics of papillary-cystic neoplasm (PCN) of the pancreas but lacking the capsule commonly observed in PCN and growing interiorly into the pancreatic parenchyma in two males and two females aged from 39 to 51. These tumors contrasted with typical encapsulated PCN that showed extrapancreatic growth and was detected as a palpable abdominal mass in young women. These four tumors, though impalpable, were all detected by nodular images of calcification in abdominal plain X-ray. These tumors had a mean diameter of 3.1 cm (ranged 1.7-4.5), were confined within the pancreatic parenchyma, and showed central fibrosis accompanied by dystrophic changes such as calcification and ossification. Small necrotic cyst contiguous to the fibrous focus was also observed in the tumor in three patients. Tumor cells being similar to those of PCN proliferated invasively among the pancreatic parenchyma in papillary pattern, and pleomorphic atypism was observed in some part of the tumor in three patients. These tumors were tentatively designated calcifying-inverted variant of PCN to differentiate it from ordinary encapsulated PCN. Although no signs of recurrence have been noticed after surgical treatment in these patients, the invasive growth pattern and the presence of pleomorphic atypism suggest higher malignancy than the ordinary PCN. The contrasting growth pattern and possible malignancy may warrant establishment of these tumors as a PCN subclass.

The efficacy of peroral transpapillary pancreatoscopy (POPS), pancreatic duct biopsy, and brush cytology with a special reference to the mode of extension of pancreatic cancer

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We experienced 107 resected cases of pancreatic tumors (90 cases were malignant, and 17 cases benign). Macroscopically they were classified into three types; solid type (78%), cystic type (27%), and intraductal type (8%). We attempted POPS for 19 pts, and success rate of visualization was high (18/19). Intraductal tumors which looked like fish eggs were clearly seen for most

of cases whose tumors exsisted in the main pancreatic duct. By pancreatic duct biopsy and brush cytology, correct diagnosis was histologically made in 50% (8/16), 64% (8/14), respectively. In case of cystic type and intraductal type, duct biopsy is more effective than cytology, but in case of solid type cytology is more effective than biopsy. We concluded that it is necessary to select three methods mentioned above according to the type of pancreatic tumors for early diagnosis.

The cytological brushing to pancreatic cancer

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ERCP has become one of the important examination methods for pancreatic cancer. In fact, the diagnostic ability of ERCP for small intrapancreatic lesions is good, however, there are still some cases who receive pancreatectomy only on the basis of the diagnosis suspecting carcinoma. Therefore, it is necessary to improve the diagnostic ability of ERCP.

In the present study, a trial was to insert cytodiagnostic brushes and biopsy forceps after performing EST. By applying, it is easy to insert the cytodiagnostic brush and biopsy forceps. Although EST is originally a technique to be utilized for the treatment of the calculus in the biliary tract, the present technique of ours is called "diagnostic papillotomy" because it is also applied to the diagnosis. Using this method, a small pancreatic cancer (10mm size) was found, and the diagnostic ratio of cytology for pancreatic cancer was 92%. The technique for this method is shown and the case reports are made.

Magnetic resonance (MR) imaging of pancreatic cancer

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A retrospective analysis was made to evaluate the diagnostic ability of magnetic resonance (MR) imaging for normal pancreas and pancreatic cancer.

Subjects and Methods: 1) 19 normal subjects; 2) 24 patients with pancreatic cancer, consisting of 4 patients with T1 (<2cm in diameter), 5 with T2a (<3cm), 10 with T2b (<4cm), 4 with T3 (<6cm), and 1 with T4 (>6cm). MR imaging was performed on a Vista MR (Picker Inc.) with a superconducting magnet operating at 0.256 Tesla and 0.5 Tesla.

Results: 1) Visualization rates of the normal pancreatic gland were 84%, 100%, and 89%, in the head, body and tail of the pancreas, respectively. Those of vessels were 100% in each of the portal vein, splenic vein, and superior mesenteric artery, 21% in the common hepatic artery, 53% in the common bile duct, and 0% in the pancreatic duct. 2) In 24 patients with pancreatic cancer, morphological enlargement could be observed in none of 4 patients with T1, 4 of 5 with T2a, 10 of 10 with T2b, 4 of 4 with T3, 1 of 1 with T4, respectively. The tumor was identified as a low intensity area in 1 of 4 cases with T1, 3 of 5 with T2a, 7 of 10 with T2b, 3 of 4 with T3, and none of 1 with T4, respectively. Tumor identification rate was 88%. Accurate diagnosis of the relationship between the portal vein and tumor was obtained in 19 of21 cases.

Discussion: Advanced pancreatic cancer could be identified easily on MR image, and occasionally, asmall cancer of the pancreas could be visualized as a low intensity area within the pancreatic gland. In addition, since blood vessels show a marked structure without signal on MR images, MR imaging is useful for diagnosis of vascular involvement. This modality is effective for diagnosis of pancreatic cancer and is expected to be used for routine examination of pancreatic cancer.

Novel application of monoclonal antibodies and anti-idiotypic antibodies for sero-diagnosis of pancreatic cancer

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We have developed two novel monoclonal antibodies YH206 (IgM) and MUSE11 (IgG2a) which can effectively detect tumor-associated antigens in the sera of patients with pancreatic cancer. Western blot analysis revealed that the antigen YH206 is of over 1000kd glycoprotein and the antigen MUSE11 is of 300kd glycoprotein. These two molecules are different from pancreatic cancer associated antigens descrived previously such as CA19-9, Span-1, SLX or CEA. Fifteen of 34 (44%) patients with pancreatic cancer had high serum YH206 levels by enzyme immunoassay, whereas 12 patients with chronic pancreatitis had no elevated levels. Serum MUSE11 levels were elevated in 25 of 43 (58%) patients with pancreatic cancer, 2 of 19 (11%) patients with chronic pancreatitis. Interestingly, 2 of 3 patients with T1 pancreatic cancer showed positive in the levels of the serum MUSE11. In addition, anti-idiotypic monoclonal antibody AI206 (IgG1) against YH206 antibody was developed and it was shown to be a useful reagent for detection of YH206 antibody in the sera of pancreatic cancer patients, especially for sero-diagnosis of pancreatic cancer patients revealed the low YH206 antigen levels in the sera. Therefore, these three combination assay is powerful tools for sero-diagnosis of pancreatic cancer.

Symposium-4

Organ correlation in digestive diseases

Moderators: Tadasu TSUJII and Tadashi TAKEUCHI

Mechanism for functional perturbation of extrahepatic tissues during hepato-biliary diseases

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Metabolism of glutathione (GSH), a naturally occurring antioxidant, occurs via interorgan cooperation in which liver and kidney play an important role. To understand the mechanism by which functions of extrahepatic tissues are easily perturbed in patients with hepato-biliary diseases, we studied changes in GSH status in liver, kidney and stomach, and in the occurrence of stress-induced acute gastric mucosal injury (AGML) in bile-duct-ligated rats. When animals were given water-immersion-restraint stress, AGML was rapidly induced. Intravenous administration of a superoxide dismutase derivative, which circulates bound to albumin and accumulates in an injured tissue whose local pH is decreased, markedly inhibited the occurrence of AGML, suggesting the involvement of oxidative stress in the pathogenesis of AGML. During a few days after bile-duct-ligation, AGML was markedly inhibited; however, it was significantly enhanced thereafter. Kinetic analysis revealed that hepatic GSH levels changed after bile-duct-ligation; it showed a mirror-image with the occurrence of AGML. Administration of a loading dose of GSH markedly inhibited the occurrence of AGML, while it was enhanced significantly by deplet-

ing hepatic GSH by buthionine sulfoximine, a specific inhibitor for GSH synthesis. The elevated level of bilirubin seemed to perturb the mechanism by which hepato-renal GSH levels are controlled. Thus, hepato-renal GSH levels markedly increased during a few days after bile-duct-ligation and decreased thereafter. Kinetic analysis revealed that change in GSH status in liver and kidney plays a critical role in protecting extrahepatic tissues, such as the stomach, from oxidative stress occurring in hepato-biliary diseases.

Metabolic relationship between liver and pancreas or kidney

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We have studied the relationship between carbohydrate metabolism in liver and that in pancreas or kidney in rats and humans with hepatic injury. Administration of single dose of carbon tetrachloride (CCl_4) to rats caused decline of blood glucose and activity of hepatic phosphoenolpyruvate carboxykinase (PEPCK), which is one of key enzymes in gluconeogenesis in liver. Plasma immunoreactive glucagon (IRG) in patients with liver cirrhosis elevated about eight times more than in normal control, accompanied with increase in IRG with a molecular weight of about 3,500 (IRG^{3500}). Elevation of plasma IRG in cirrhotic patients after infusion of arginine was greater than that in normal control. Elevation of both plasma IRG and blood ammonia concentration in rats treated with urease were observed, and there was a good correlation with them. Decrease in blood glucose concentration and increase in blood ammonia concentration might be a signal to stimulate secretion of pancreatic glucagon. Moreover, activity of renal PEPCK in rats treated with CCl_4 significantly increased more than in normal rats, while both blood glucose and activity of hepatic PEPCK declined. The increase in activity of renal PEPCK in CCl_4-injured rats was suppressed by treatment with actinomycin D and glucose infusion. Net renal glucose release and its contribution to blood glucose in CCl_4-injured rats were found to be greater than those in control rats. These results suggest that there is a metabolic correlation between carbohydrate metabolism in liver and that in pancreas or kidney in rats with hepatic injury.

Metabolic relationship between the liver and extrahepatic organs under the condition of hepatic failure: A tracer study using 15N-labeled leucine and ammonium chloride in fulminant hepatic failure rats

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The branched-chain amino acids (BCAA) infusion therapy causes sometimes an elevation of blood ammonia concentration. In this study, we attempted to clarify the undergoing mechanism in these phenomenon using stable isotope 15N labeled leucine and ammonium chloride to D-galactosamine induced fulminant hepatic failure (FHF) rats. The procedure of animal experiments and the measurement of 15N enrichment by GC/MS in ammonia, urea, alanine and amino- and amide-nitrogen of glutamine were reported detailed previously[1-3]. 15N labeled L-leucine or ammonium chloride were infused via tail vein and the arterial blood was drown before and 5, 15, 30, 60 min after the injection.

With the 15N-leucine injection, plasma amino-15N level of glutamine rose 15 min after the injection then both of it and alanine-15N increased up to 60 min FHF rats. At the time of 60 min after the injection, plasma amide-15N level of glutamine elevated moderately. With the 15N-ammonium chloride injection, plasma amide-N level of glutamine rose 15 min after the injection followed by an elevation of urea-15N after 30 min.

These results suggest strongly that under the condition of functionally diminished urea cycle in a hepatic failure, the incorporation of 15N

into the extrahepatic glutamine pool is accelerated up to 15 min and after 30 min a larger volume of glutamine is transferred to the urea cycle followed by an increase of plasma ammonia.

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Pathogenesis of disturbed water excretion in patients with liver cirrhosis

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To investigate the mechanism of impaired water excretion in liver cirrhosis (LC), we have measured plasma antidiuretic hormone (ADH), atrial natriuretic hormone (hANP), noradrenaline (NA), substance P (SP) before and after water overload. After equilibration on a 50-85 mEq sodium diet, an i.v. water overload (5% glucose) of 20 ml/kg of body wt. was given during 1 hr. Free water clearance (CH_2O) in LC with ascites (DLC) was significantly lower than that in healthy subjects (HS, $P<0.001$) and LC without ascites (CLC, $P<0.005$). In addition, creatinine clearance(C_{cr}), maximum urine flow rate (V_{max}/C_{cr}, $(CH_2O+C_{Na})/C_{cr}$ and urinary sodium excretion ($U_{Na}V$) were significantly lower than those in HS and CLC. Before water overload, SP in LC was significantly higher than that in HS ($P<0.001$). SP in DLC was higher ($P<0.05$) than that in CLC. NA and hANP in LC were significantly higher than those in HS. ADH in DLC was not different from that in CLC. After water overload, SP and ADH remained unchanged in LC. NA and hANP increased in half cases of LC. CH_2O was positively correlated with serum albumin, cholinesterase, and negatively correlated with $ICGR_{15}$. SP was negatively correlated with CH_2O ($r=-0.70$, $P<0.001$). NA was correlated positively with SP ($r=0.63$, $P<0.005$) and negatively with CH_2O ($r=0.55$, $P<0.005$) after water overload. Conclusion: (1) Decreased CH_2O was closely related to the severity of liver disturbance. (2) Decreased C_{cr} and reduced delivery of filtrate to the distal nephron secondary to an increased sodium reabsorption in proximal tubule may be important for impaired water excretion. (3) Increased SP and the associated increased activity of the sympathetic nervous system may be responsible for impaired water excretion.

Innervation of the mesenteric lymph nodes and multiple organ microcirculatory disturbances in relation to the pathogenesis of Reilly phenomenon

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It is well known as the Reilly phenomenon that the excessive irritation of the autonomic nervous system causes hemorrhagic and necrotic changes in a variety of visceral organs. For better understanding of mechanism of this phenomenon, it is essential to further elucidate the autonomic innervation of these organs. Endotoxin (E, coli 0111 B4 difco) was directly injected into the rat mesenteric lymph nodes with a dose of 0.1mg/kg. Twenty four hrs after the administration of endotoxin, stomach, Peyer's patches and liver were subjected to macroscopic, histological, and cytochemical observations. The microvascular permeability was judged by the degree in extravasation of horseradish peroxidase (HRP). In an attempt to identify the afferent nerve fibers from the mesenteric lymph nodes, the presence of HRP reaction products was examined in the spinal cord 48hrs after the topical application of HRP into the lymph nodes. No abnormal lesions were histologically

observed and no HRP was extravasated from the microvessels in the stomach, Peyer's patches and liver following the intravenous administration of endotoxin. In contrast after the topical application of endotoxin into the mesenteric lymph nodes, the hemorrhagic and necrotic lesions were observed in all these organs with excessive extravasation of HRP from the venules and capillaries. The HRP reaction products were noted in the dosal roots of the thoracic spinal cord, indicating the presence of the afferent nerve fibers from the mesenteric lymph nodes. Histochemically the cholinergic and adrenergic nerves were distributed along the microvessels in stomach, Peyer's patches and liver. Unmyelinaled nerve endings were evident in close vicinity of the capillaries in the stomach and Peyer's patches, and of the hepatic sinusoids. In conclusion the endotoxin-induced overstimulation of the mesenteric lymph nodes induced the hemorrhagic and necrotic lesions in remote visceral organs such as the stomach, Peyer's patches and liver. This phenomenon would be caused by excessive transmission of a pathognomonic stimuli via the autonomic nerve system, resulting in the organ microcirculatory disturbances.

Autonomic disorder and multiorgan failure in liver injury—Clinical and experimental investigations—

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Multiorgan failure (MOF) in liver injury was investigated from the mode of action of plasma catecholamines (CA). (I) Clinical study: CA levels using HPLC in 56 patients with liver cirrhosis disclosed elevation of noradrenaline (NA) in 33 cases (59%). These patients showed ulcer and/or erosive lesions in upper digestive tract, platelet count below $10x10^4$/cmm and diabetic pattern in o-GTT. NA levels had no correlation with the degree of esophageal varices, however, correlated well with the evidence of upper gastrointestinal lesions, retention of body bluid and platelet count. Furthermore, the levels bore considerable relations with the degree of PO_2 as well as of 2,3-diphosphoglycerate. (II) Experimental design: Reserpine was ip injected to male Wistar rats at a dose of 0.01mg/100g bw twice daily. Four consecutive days treatment reduced the average NA and adrenaline to 25 and 30% of control, respectively. Carbon tetrachloride (CCl_4), mixed with an equal amount of olive oil, was one shot ip administered at a dose of 0.25ml/100g bw. Single injection of CCl_4 induced centrilobular bleeding and necrosis of the liver without MOF. On the other hand, reserpine pretreatment prominently aggravated the hepatic lesions concomitant with MOF, such as brain, lung, stomach, small intestine and spleen, highly suggesting microcirculatory disorder. It is concluded that plasma CA play a large part in regulating microcirculatory system in hepatic disorder, and the role of sympathetic nervous system along with CA must virtually be emphasized.

Changes of gallbladder motor function after gastrectomy

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The purpose of this study is to observe changes of gallbladder motor function in respense to the exogenous or endogenous stimulus after gastrectomy.

Methods: A) Exogenous study: Fasting gallbladder area and maximal gallbladder contraction rate in response to caerulein (0.2μg/kg i.m.) were measured ultrasonographically in patients with gastric cancer before 1 month and 12 months after gastrectomy. B) Exogenous study: Gallbladder contraction (by ultrasonography) and plasma levels of CCK (by radioimmunoassay), were measured simultaneously after clinimeal ingestion.

Results: A) Caerulein study: Although maxi-

mal gallbaldder contraction rate (MGCR) was reduced to 56±6% of pre-gastrectomy levels (100%) 1 month after gastrectomy (n=27), MGCR after gastrectomy attained almost the same level as before gastrectomy at 12 months (97±7%, n=30). B) Clinimeal study: Before gastrectomy, MGCR was observed at 30 minutes with the contraction plase lasting for 70 minutes. On the other hand, MGCR was observed at 30 minutes 1 month after gastrectomy (n=6), however, with no contraction phase, leading to the early refilling of the gallbladder. This tendency was also observed even at 12 months (n=9). Significant correlation was observed between CCK release and gallbladder contraction in both pre-and-post gastrectomy periods.

Conclusion: Although gallbladder sensitivity was reduced after gastrectomy, MGCR was gradually recoverd, attaining almost the same level as before gastrectomy within 12 months. This study demonstrates that the release of CCK is the chief mechanism by which ingestion of a fatty meal causes contraction of the gallbladder after gastrectomy as well as before gastrectomy. The early beginning of the refilling and lack of the contraction phase of gallbladder after gastrectomy might induce the cholestasis, which could be one of the causes of cholecystitis or stone formation after gastrectomy.

Effects of gastrectomy on the motility of sphincter of Oddi

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Change in the motility and response to caerulein of sphincter of Oddi (SO) after gastrectomy was investigated in dogs to elucidate the causative mechanism of gallstone formation after gastrectomy.

The resistance and frequency of phasic contraction of SO after gastrectomy increased significantly compared with those after sham operation and before gastrectomy ($P<0.05$, $P<0.01$). Although caerulein (10ng/kg, i.v.) caused inhibitory effect on the SO motility in almost all control of gastrectomy group and sham operation group, it did not induced inhibitory effect but excitatory effect on SO motility after gastrectomy. There was significant difference in the diameters of gallbladder and choledochus between before and 1 month after gastrectomy ($P<0.05$, $P<0.01$). There was no significant difference in maximal contraction of gallbladder between sham operation group and gastrectomy group.

The present study suggested that dysfunction of SO was induced by gastrectomy, resulting in the elevation of biliary pressure and impared delivery of bile into duodenum.

A significant role of endogenous secretin on relationship between gastric and pancreatic secretion

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A physiological role of endogenous secretin on relationship between gastric and pancreatic secretion was studied. Postprandial plasma secretin and gastrin concentrations were determined in healthy human volunteers, who received meal alone, meal plus intravenous (IV) injection of ranitidine (50 mg) or meal plus IV infusion of secretin (0.03 CU/kg-hr). Plasma secretin increased after ingestion of a meal, and ranitidine significantly suppressed the increase in plasma secretin concentration after a meal. Postprandial response of plasma gastrin augmented markedly by treatment with ranitidine, however it was inhibited by IV infusion of secretin in a dose. Furthermore, effects of either IV secretin infusion (0.05 CU/kg-hr) or intraduodenal (ID) oleic acid emulsion (1 mmole/hr, pH 6.5) on gastric acid secretion stimulated by IV pentagastrin (0.3 μg/kg-hr) and on plasma secretin concentrations were studied in anesthetized rats. Gastric acid secretion was sup-

pressed significantly in 66.3% or 42.4%, by either IV infusion secretin or ID infusion of oleic acid, respectively. On the other hand, ID administration of oleic acid resulted in significant increases in pancreatic exocrine secretion and plasma secretin concentration from 1.2±0.1 to 3.9±0.2 pM.

In conclusions, endogenous secretin plays an important role on inhibition of gastrin release and gastric acid secretion in the postprandial state. It is suggested that secretin is one of enterogastrone.

The role of gastric juice, pancreatic juice and bile in the duodenum was investigated in endogenous secretin release and exocrine pancreatic secretion in P-F dogs and human subjects

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The effect of gastric acid on endogenous plasma secretin release (EPSR) and exocrine pancreatic secretion (EPS) was investigated in P-F dogs with cimetidine administration or total gastrectomized patients in postprandial state. For the lack of gastric acid from the duodenum EPSR and EPS remarkably diminished in postprandial state in P-F dogs and gastrectomized patients. The effect of bile administration into the duodenum was investigated on EPSR and EPS in P-F dogs. Bile stimulated EPSR and EPS in less degree than stimulated by gastric acid.

The lack of pancreatic juice from the duodenum was investigated in P-F dogs and pancreatic duct ligated dogs in postprandial state. Exclusion of pancreatic juice from the duodenum stimulated EPSR and EPS through a negative feedback mechanism.

Conclusion: Endogenous secretin release and exocrine pancreatic secretion are under the control in parts of gastric acid, bile and pancreatic juice in the duodenum.

Stimulatory effect of monitor peptide and human pancreatic secretory trypsin inhibitor on pancreatic secretion and cholecystokinin release in conscious rats

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The stimulatory effects of monitor peptide (MP) which was recently purified from rat bile-pancreatic juice[1], on cholecystokinin (CCK) release and pancreatic exocrine secretions were examined in conscious rats with external bile and pancreatic fistulae. Furthermore, the sequence of MP has some homology with hPSTI, the effects of these two materials were compared to each other. Under the conditions of both PJ diversion and PJ diversion with Trasylol infusion in order to completely eliminate luminal protease activities, MP (0.9μg/rat) showed the stimulatory effect, but hPSTI did not show any stimulatory effect on pancreatic secretion. Plasma CCK levels produced by MP were significantly higher than those by hPSTI. It was concluded that MP has a strong species specificity and that MP could stimulate CCK release and pancreatic exocrine secretions, not only via inhibiting luminal protease activities but also probably having a direct effect.

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Panel discussion-1

Diagnosis and treatment of small liver cancer

Moderators: Kyuichi TANIKAWA and Ryuji MIZUMOTO

Imaging diagnosis of small liver cancers: with special reference to differential diagnosis from non-cancerous nodular lesions in cirrhotic liver

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The imaging findings of 54 cases with small liver cancer (less than 2cm in diameter, solitary) and 19 non-cancerous nodular lesions (NCNL) in cirrhotic liver which were visualized on ultrasonography (US), computed tomography (CT) or hepatic arteriography were analyzed in comparison with histological findings. On histology, the development of capsule and septums was poor in small liver cancers, therefore, the imaging findings of small liver cancers were occasionally non-specific, especially in small liver cancers less than 1.5cm in diameter (more than 70% of cases). The imaging findings of NCNL were also non-specific and its differentation from small liver cancer by US, CT and arteriography was considered to be difficult. On the other hand, CT during arterial portography (CTAP) was very useful in differentiating between them. In 93% of small liver cancers, no definite portal perfusion was seen on CTAP, on the contrary, it was verified in 94% of NCNLs. We also analyzed the findings of magnetic resonance imaging (MRI) in patients with resected small liver cancer and NCNL and found that MRI was very useful and unique in diagnosing small liver cancers and differentiation between cancer and NCNL.

Histological diagnosis and percutaneous ethanol injection therapy (PEIT) of small hepatocellular carcinoma by ultrasound-guided fine needle puncture

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We studied about the histological diagnosis and treatment of small (≦ 2 cm) hepatocellular carcinoma (HCC) by US-guided fine needle puncture. From May 1985 to Dec. 1987, US-guided fine needle (21-G, MAJIMA NEEDLE) biopsy was performed using the new technique for histological diagnosis of 348 hepatic modules in the high risk group (chronic liver diseases) of HCC. The PEIT was performed in 50 small HCC cases for recent 4 years. The results were as follows : 1) In 105 tumor-like nodules smaller than 10 mm in diameter, 25 (23.8%) solitary primary lesions were HCC. 2) We originally named the characteristic marginal hyperechoic rim as a "Bright Loop" pattern in HCC. The "Bright Loop" pattern of HCC is mainly dependent upon the fatty change and pseudograndular formations. 3) The 2-years, 3-years, and 4-years survival rate by Kaplan-Meier Method were 92.3%, 73.9%, and 73.9%, respectively. 4) The 3-years survival rate were 100% in the cases with early liver cirrhosis (Child's-A). Thus US-guided fine needle puncture are very important for early diagnosis and treatment of small HCC.

Early diagnosis and treatment of hepatocellular carcinoma

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Diagnostic accuracies of the clinical follow-up system and ultrasonically-guided fine-needle aspiration biopsy in early detection of hepatocellular carcinoma (HCC) and clinical values of lipiodol-cisplatin Sandwich therapy for HCC were examined.

622 patients with liver cirrhosis or chronic hepatitis were followed-up by the system using ultrasonography and AFP every 3 or 6 months for 16 months. Nineteen HCC were found by this system. These HCC were somewhat smaller than those found in our outpatient clinic. In sixteen of them (84.2%), TAE were performed, and in eight (42.1%) complete resection could be performed.

We developed a heparinized fine-needle aspiration biopsy under ultrasonic guidance. Diagnostic accuracies of the method for HCC were cytologically 90.4% and histologically 89.9%. Overall accuracy was 94.5% (69/73). We also developed a lipiodol-cisplatin Sandwich therapy for HCC. One-, two- and three year cumulative survival rate of patients with unresectable HCC by this treatment were 72.3%, 45.1% and 29.8%, respectively.

Our system of diagnostic and therapeutic techniques is extremely effective for early diagnosis and curative treatment of HCC.

Preclincical diagnosis of hepatocellular carcinoma by analysis of lectin-reactive molecular species of AFP

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Tumor marker diagnosis of hepatocellular carcinoma (HCC) for patients with elevated serum levels of α-fetoprotein (AFP) without localized lesions of the liver, even after using several modalities of diagnostic imaging for detection of HCC, was attempted by analysis of the lectin reactivity of AFP. Lectin affinity electrophoresis coupled with our sensitive detection method of antibody-affinity blotting was used for this purpose for sera with AFP levels above 50 ng/ml. Sensitivities of LCA-A-reactive AFP-L3 and E-PHA-reactive AFP-P4 as markers of HCC were 78% and 88%, respectively, at a specificity of 99.9%, which was established against chronic hepatitis and liver cirrhosis with elevated AFP and without development of HCC at least for one year. Since the increase of AFP-L3 and AFP-P4 was complementary, 97% of HCC cases were positive for either of those markers. Four patients with liver cirrhosis having increased proportions of AFP-L3 and/or AFP-P4 without demonstrable hepatic lesions of HCC all developed visible tumors within 1 month, 7 months, 8 months, and 1 year and 10 months, while only one of 44 patients with chronic hepatitis and liver cirrhosis having increased levels of AFP but not increased proportions of AFP-L3 and AFP-P4 evolved HCC within one year of follow-up period without marked changes in lectin reactivity of AFP. Of the four seromarker-positive and imaging-negative HCC patients, two had an infiltrative type of HCC and the remaining two had an early stage of HCC. The results indicate the usefulness of the combined evaluation of AFP-L3 and AFP-P4 for preclinical diagnosis of HCC.

Clinical pathological effects of preoperative embolization therapy for small liver cancer

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To identify possible ways to treat small liver cancers less than 2 cm in diameter, we compared the clinical and pathological findings in patients with a recurrence following liver resection (group with recurrence) with such findings in patients without (group without recurrence). The clinical stage I or II. In most patients who later had a recurrence, there was invasion

of the capsule or the surrounding hepatic tissue at the time of resection; therefore it is important to treat such invasion. The patients with invasion should be treated by radical surgery, with selective removal of the tumor-bearing area, such as by subsegmentectomy or segmentectomy. Preoperative transcatheter arterial embolization (TAE) was not effective in preventing the recurrence, so it is necessary to enhance the effect of TAE by portal vein embolization.

Surgical treatment for small liver cancer

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Ten percent (34) of 341 resected hepatocellular carcinomas (HCC) were small HCCs defined as solitary HCC 2cm or less in the greatest dimension. Of 34, 33 were developed in the injured livers such as chronic active hepatitis, hepatic fibrosis and cirrhosis. The incidence of microscopic portal vein invasion was 29.4% in cases with small HCC, whereas those in cases with solitary HCC 2~5cm in diameter and multiple HCC 5cm or less in diameter were 39.6% and 57.0%, respectively. The five-year survival rate of small HCCs after surgery was 92.0% which was significantly better than those of the two other categories of HCC. Anatomical resection was applied in 13 cases with small HCC and non-anatomical resection was in 21 cases. The survival rates and the incidences of recurrence in these two groups by the surgical procedure did not show any significant differences. In six cases which were preoperatively diagnosed as solitary, the second or third minute modules were detected in the surgical specimens. As image diagnosis for hepatic tumor is not absolutely perfect, resection for small HCC should be anatomical such as subsegmentectomy when the liver reserve is allowed.