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T. Takeuchi, President

PART 1 Abstracts of Special Lectures

H. G. Beger, W. Y. Chey, P. M. Pour, T. Sugimura

PART 2 Abstracts of Educational Symposia:

1. Pancreatic Surgery Today
2. New Approaches for the Management of Acute Pancreatitis
3. Possible Role of CCK for the Development and Progression of Acute Pancreatitis and Therapeutic Application of CCK-Antagonist
4. Assessment of Pancreatic Exocrine Insufficiency and Its Treatment
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6. Assessment and Treatment of Severe Acute Pancreatitis

PART 3 General Abstracts from IAP'98 Tokyo

INTERNATIONAL DOCUMENTATION SYSTEM FOR PANCREATIC CANCER (IDS)
- A CHANCE TO OVERCOME INTERNATIONAL BARRIERS?
H. G. Beger, D. Birk, P. Hermanek* and the International PCIDS Group
Department of General Surgery, University of Ulm, Germany
*Department of Surgical Pathology, University of Erlangen, Germany

The ability to compare treatment results is essential for the proper evaluation of treatment protocols. Especially in the case of exocrine pancreatic cancer (EPC) different classifications and documentation systems hinder the comparison between institutions and do not allow multicenter analysis across the world. This fact might explain the vastly different results of similar therapeutic trials and studies. In the currently used classifications included features as well as terminology and description vary greatly. To stage pancreatic malignancies the UICC criteria were first published in 1987, these rules were predominantly based on the suggestions of the "AJCC Cancer of the Pancreas Task Force" and have since not been changed. In Japan a different staging system has emerged and was published by the Japan Pancreas Society in 1986. The Japanese classification system is considered to be in many points representative of the tumor biology of pancreatic cancer on the basis of our present knowledge, whereas the UICC classification of stage II is weak. The major difference between the two classifications concerns the evaluation of local tumor growth and the extent of lymph node involvement. Unfortunately most attempts to "restage" Western patients postoperatively according to JPS criteria or vice versa, in order to compare treatment results, has not resulted in a clearer understanding. Much on the contrary, the results were frequently confusing since not comparable data were nevertheless retrospectively compared. Thus, a uniform *International Documentation System* (IDS for EPC) is needed, leading to standardized data acquisition and biometric analysis of outcome. IDS for EPC should serve as a standard format for worldwide data acquisition and documentation and thereby become the common language to describe diagnosis, treatment, pathology and outcome of pancreatic cancer patients who underwent surgical therapy. IDS for EPC should enable interinstitutional data exchange from different staging systems, comparisons between institutions on an international basis, quality management in clinical practice and studies, reliable insight into tumor biology and differences in growth patterns. The present form of IDS was designed by the authors with the help of leading surgeons and pathologists from the USA, Japan and Europe (PCIDS-Group) with a vast background of pancreatology. A classification matrix with coding instructions has been defined, supported by a software program (based on Microsoft Access C) which allows simplified data acquisition, statistical analysis as well as automated stage grouping in UICC and JPS classification. The IDS of EPC is based on the Japanese experience about the pattern of cancer dissemination including tumor size, N1-, N2-lymph node involvement, retro-pancreatic spread, perivascular growth, peritoneal spread and haematogenous metastases. From the first contact with the patient through all diagnostic and therapeutic measures including follow-up IDS enables a compact and easy to use tool for prospective data acquisition and exchange on an international basis.

THE LINK BETWEEN EXOCRINE PANCREATIC CANCER AND THE ENDOCRINE PANCREAS

PM. Pour, Liu G, Schmied B

UNMC/Eppley Cancer Center, Univ. of Nebraska Med. Center, Omaha, NE

Introduction. Observations in the hamster pancreatic cancer model and in patients with pancreatic cancer have indicated a relationship between cancer and the endocrine pancreas. We have performed studies to clarify this issue.

Methods. Syrian Golden hamsters treated with BOP, transplanted hamster pancreatic islets, cultured human and hamster islets, and surgical or autopsy material from pancreatic cancer patients were used.

Results. a) Studies in the hamster model: 1) Most invasive ductal cancers developed within islets. 2) Over 90% of induced ductal cancers contained endocrine cells. 3) Destruction of pancreatic β cells with streptozotocin or alloxan inhibited pancreatic carcinogenesis. 4) Genetically diabetic hamster strain with atrophic islets was resistant to pancreatic carcinogenic effect of BOP; whereas, the genetically non-diabetic strain with intact islets was not. 5) Induction of nesidioblastosis significantly enhanced the incidence and numbers of pancreatic cancer. 6) BOP induced tumor in the submandibular glands where homologous islets were transplanted but not in those without islet transplantation. 7) Treatment of isolated hamster islets in culture with BOP led to the development of malignant cells with invasive potential in vivo when transplanted into the subcutaneous tissue, pancreas or submandibular gland of recipient hamsters. 8) Hamsters with cancer show serum hormone abnormalities. **Studies in humans:** 1) As in hamsters, malignant glandular structures were found in the pancreas of patients with or without pancreatic cancer. 2) Over 90% of pancreatic cancer contained variety of pancreatic endocrine cells. 3) No cancers have ever been recorded in type I diabetic patients. 4) Treatment of isolated human islets in culture with BOP causes malignant transformation. 5) Pancreatic cancer patients show hormonal abnormalities similar to that found in hamsters.

Conclusion. Certain populations of pancreatic islets (most probably the stem cells) present cancer progenitor cells. Pancreatic carcinogenesis involves both the exocrine and endocrine pancreas.

ULCEROGENIC PANCREATIC TUMOR SYNDROME -1998

W.Y. Chey*, T.M. Chang, Y. Song

Konar Center for Digestive and Liver Diseases, University of Rochester Medical Center, Rochester, NY, USA

Since our original report of 4 patients in 1984 who had islet cell tumors, massive gastric acid hypersecretion, peptic ulceration but normal circulating gastrin level (eugastrinemia), we have found 20 with eugastrinemia among 46 consecutive patients with ulcerogenic pancreatic tumor syndrome. The remaining 26 patients had hypergastrinemia. These observations suggested that the prevalence of ulcerogenic pancreatic tumors with euglycemia may be as frequent as that with hypergastrinemia. Characteristics of the ulcerogenic pancreatic tumor syndrome with eugastrinemia are: 1) unlike gastrinoma, the tumors contain only a minimal amount of gastrin, 2) the tumor and plasma contain a non-gastrin acid secretagogue which is a peptide (NGASP), 3) biological activity of NGASP is abolished by trypsin whereas that of gastrin is not, 4) incubation with antibody to human synthetic gastrin did not affect bioactivity of the peptide while that of human gastrin was completely abolished, and 5) the release of histamine by gastrin from ECL cells in rat gastric fundus is blocked by a CCK-B receptor antagonist whereas histamine release by NGASP is not. It is of considerable interest to note that the dose response of acid secretion to NGASP in rats receiving pentagastrin (PG) in a threshold dose was significantly greater than that achieved by NGASP alone. Similarly, the dose response to PG combined with a threshold dose of NGASP was significantly greater than that produced by PG alone. Likewise, maximum acid secretion by PG was potentiated by NGASP and vice versa. Thus it is likely that circulating gastrin and NGASP may potentiate each other to produce greater acid secretion than that produced by either one of the two secretagogues in ulcerogenic pancreatic tumor syndrome. NGASP is being purified currently from islet cell tumors. Through gel filtration and several HPLC steps, it is now purified to near homogeneity. Final purification and structural determination and synthesis of the peptide will allow development of radioimmunoassay of NGASP. Then, early detection of this tumor syndrome will be possible.

1998 PERSPECTIVES IN PANCREATIC CANCER RESEARCH

Takashi Sugimura

National Cancer Center, Tsukiji, Chuo-ku, Tokyo, Japan

Cancer is a disease of DNA, reflecting "Multiple genetic alterations", "Multiple steps of carcinogenesis", "Multiple carcinogenic xenobiotics and autotoxins", and "Multiple genetic backgrounds". Epigenetic mechanisms including methylation of DNA also might be involved in some steps. Based on the knowledge which has accumulated, multiple approaches to cancer therapy with multiple target molecules and multiple cancer prevention measures are now feasible. Pancreatic cancer is one of the most dreadful malignancies which afflict mankind. Although the genes involved are multiple and highly complex in their combinations, perturbed signal transduction resulting in abnormalities of cell cycle checkpoints and cell-cell / cell-stroma interactions explain most of phenotypes in pancreatic cancer. In addition, examples of paraneoplastic hormone hyperproduction in some malignancies of the pancreas are noteworthy. With the information available, molecular mechanisms of pancreatic carcinogenesis, possible prevention strategies, and advances in molecular diagnosis and treatment will be reviewed and discussed.

Yamada, H., Yoshida, T., Sakamoto, H., Terada, M. and Sugimura, T. Establishment of a human pancreatic adenocarcinoma cell line (PSN-1) with amplifications of both c-myc and activated c-Ki-ras by a point mutation. *Biochem. Biophys. Res. Commun.*, 140, 167-173 (1986).

Sugimura, T. Multistep carcinogenesis: A 1992 perspective. *Science*, 258, 603-607, 1992.

Aoki, K., Yoshida, T., Matsumoto, N., Ide, H., Sugimura, T. and Terada, M. Suppression of Ki-ras p21 levels leading to growth inhibition of pancreatic cancer cell lines with Ki-ras activation but not those without Ki-ras mutation. *Molecular Carcinog.*, 20, 251-258 (1997).

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RATIONALE OF THE SO-CALLED EXTENDED RESECTION FOR PANCREATIC INVASIVE DUCTAL CARCINOMA

M. Imamura, R. Hosotani, M. Kogire
Dept. Surgery & Surgical Basic Science, Kyoto Univ., Kyoto, JAPAN

Introduction: Long-term survival of surgically treated patients with pancreatic invasive ductal cancer (pancreatic ductal cancer) has remained low, and five-year survival rate has been lower than 10%. Microscopic curative resection is often very difficult to achieve in most of the pancreatic cancers, because of widely-spread lymph node metastases, definite retroperitoneal invasion and wide spread of cancer cell invasion through the nerve plexus. Clinical staging with imaging techniques is still difficult owing to the very invasive and hematologically metastatic characteristics of this cancer. It is, thus, difficult to preoperative or intraoperative estimate of the extent of the curability by surgery. For these reasons we have rather routinely performed a so-called extended resection of pancreatic ductal cancer, which includes 1) dissection of a part of the lymph nodes along the abdominal aorta with group 2- lymph nodes, 2) cleaning of nerve plexus along the common hepatic artery (or splenic artery), the celiac axis, and a part of the superior mesenteric artery with pancreatic head plexus I and II, 3) resection of a part of the celiac ganglions, and 4) PW(-) resection. **Patients and Results:** We have performed macroscopically curative resection of the invasive ductal pancreatic cancer in 141 patients (median age: 63, head cancers: 113, body and tail cancers: 28, stage I: 6, stage II: 4, stage III: 28, stage IVa: 67, stage IVb: 26). Following results were obtained; 1) The R0 resection is essentially necessary for long-term survival. 2) Comprehensive stage, curability and irradiation are clearly independent prognostic factors (Cox's proportional hazards model). 3) Patients without lymph node metastasis showed a significantly better survival curve than those with node metastasis; however, those with lymph node metastasis have also been alive more than three years. 4) The incidence of plexus invasion increased with the size and the extension of the cancer, and plexus invasion was observed in 20% of the small cancer of less than 2 cm in diameter. 5) Patients who underwent intraoperative irradiation after the resection showed higher survival rate than those with surgery alone. 6) Postoperative regional chemotherapy with continuous 5-FU infusion decreased the hepatic metastasis within 6 months. 7) For improvement of the postoperative nutritional state, preserving the whole stomach (PpPD) seems to be useful. **Conclusions:** These findings, presumably, suggest that the local recurrence of pancreatic cancer might possibly be controlled by the extended resection and the intraoperative irradiation, and the early development of hepatic metastases might be controlled with regional chemotherapy. We will present a video of our method of resection and reconstruction for the pancreatic invasive cancer.

MODIFIED STANDARD PANCREATODUODENECTOMY FOR THE TREATMENT OF PANCREATIC HEAD CANCER

Y. Kawarada*, B. C. Das, M. Tabata, T. Naganuma, S. Isaji, H. Yokoi
1st Department of Surgery, Mie University School of Medicine, Mie, Japan

Since 1980 extended surgery has been used to treat pancreatic cancer in many institution in Japan in the hope of curative resection and good outcome. The resection rate increased, but the final outcome was unsatisfactory, and instead the question of postoperative quality of life (QOL) following extended surgery has become a burning issue. During the past 22-year period (1976.10 - 1997.5) 168 of the 187 patients with invasive pancreatic ductal carcinoma were treated surgically at Mie University Hospital. There were 3 groups of patients: an early period group (1976.10 - 1981.4, n=34), a middle period group (1981.5 - 1993.3, n=100), and a late period group (1993.4 - 1997.5, n=34). The standard operation (pancreatoduodenectomy with D1 lymph node dissection) was performed in the early period, extended operations (pancreatoduodenectomy with D2 lymph node dissection) were performed in the middle period, and a modified standard operation (pancreatoduodenectomy with D1 lymph node+ α dissection) was performed in the late period. D1 dissection is similar to dissection up to the N1 level in the UICC classification. "D2 dissection" means dissection of lymph nodes up to the para-aortic region. Our "modified standard method" means dissection of the anterior pancreaticoduodenal (APD), posterior pancreaticoduodenal (PPD), pyloric (PY), hepatoduodenal ligament (HDL), common hepatic artery (CH), middle colic vessel (MC) lymph nodes and half of the superior mesenteric (SM) lymph nodes. Thus, the lymph node dissection level in the modified standard procedure is between the level in the standard and extended procedure, but the pancreatoduodenectomy is the same as usual. We consider the previous standard operation to be a less curative resection procedure, and the extended operation to be curative resection, but a high-stress operation. Accordingly, we have modified the surgical procedure (modified standard operation) in our recent cases out of consideration for the patients QOL. I would like to show our modified standard procedure actually being performed on one of our patients in the video tape presentation.

PANCREATODUODENECTOMY AND POSTOPERATIVE LIVER PERFUSION CHEMOTHERAPY FOR ADENOCARCINOMA OF THE PANCREAS

O. Ishikawa, Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan
Introduction: Both locoregional recurrence and hepatic meta-stasis are major causes of cancer death after resection of adenocarcinoma of the pancreas. Thus, in resection of pancreatic head cancer, we have performed a wide range of lymphatic and connective tissue clearance plus postoperative liver perfusion chemotherapy (LPC). **Operative procedure and postoperative LPC(Video):** During operation, the major vessels such as the superior mesenteric artery, celiac truncus, aorta are skeletonized to clearly remove the surrounding connective tissues and lymph nodes (Extended pancreatotomy). The portal vein, if cancer invasion is suspected, is also resected together with the pancreatic head without performing the "tunneling" procedure. Each one catheter is placed in the hepatic artery and one of the vein in the mesentery. Postoperatively, 125 mg/day of 5-fluorouracil is infused via each of the two routes continuously for 4 weeks (LPC). **Results:** The 5-year survival rate in our extended pancreatotomy plus LPC was 41% which was significantly higher than 24% of extended pancreatotomy alone or 8% of the conventional pancreatotomy alone. This procedure has succeeded in producing the 5-year survivors even among the patients with nodal involvement or portal vein invasion. However, it is almost impossible for more advanced cancer which involved any arteries or the lymph nodes which were not adjacent to the pancreatic head. A watery diarrhea is the most troublesome complication. **Conclusion:** An extended pancreatotomy in combined with LPC should be more actively performed in resection of pancreatic cancer, but a careful attention is needed on the patients' selection.

PYLORUS-PRESERVING PANCREATODUODENECTOMY WITH PORTAL VEIN RESECTION AND INTRAOPERATIVE RADIOTHERAPY

S. Takahashi, J. Saitoh, S. Hayatsu, K. Aiura, M. Kitajima, Y. Ogata*
Department of Surgery, Keio University School of Medicine, Tokyo, Japan.
Department of Surgery, Tochigi Cancer Center*, Utsunomiya, Japan.

Various attempts are currently being made to determine the best method of treating pancreatic head cancer, which has the poorest treatment outcome of cancer in the peripapillary lesion. The indications for pylorus-preserving pancreatoduodenectomy (PPPD) as a treatment for pancreatic head cancer are currently being debated from the standpoint of curability.

We began performing PPPD in 1983 as a method of treating only poor risk or non-curative cases, and later we enlarged the indications. As a result, PPPD is now considered capable of serving as the standard procedure for cancer of the head of the pancreas if the following 3 conditions are suitable: (1) absence of metastasis to the supra and/or infra-pyloric lymph nodes, (2) no direct invasion of the duodenum or stomach, and (3) the absence of extensive invasion anteriorly, so that removal is possible within the extent of resection by PPPD. In accordance with this policy, PPPD combined with D2 dissection has been performed in 29 patients thus far, and no problems have been found in terms of the curability of PPPD when the results were assessed in comparison with 62 cases of ordinary PD, with no significant differences between the two groups in stage distribution, surgical mortality, hospital deaths, incidence of postoperative complications, or postoperative survival time.

Assessment of the autopsy findings in pancreatic cancer resection cases has reconfirmed the importance of prevention of local recurrence and liver metastasis, and we have been performing intraoperative irradiation since 1985 and continuous administration of anticancer drugs via a portal catheter since 1986.

We will watch a video of PPPD in a patient with pancreatic head cancer and see that retroperitoneal dissection including combined resection of the portal vein, D2 lymphnode dissection associated with resection of extrapancreatic nerve plexus, and we will also see intraoperative irradiation, portal vein catheterization, and digestive tract reconstruction by the Imanaga procedure.

EFFECT OF IS-741 (A NEW SYNTHETIC ANTI-INFLAMMATORY AGENT) ON ACUTE NECROTIZING PANCREATITIS IN DOGS: SIGNIFICANCE OF ITS INHIBITORY EFFECT ON CYTOSOLIC PHOSPHOLIPASE A2

S. Isaji, T. Iida, J. Hayashi, T. Higashiguchi, H. Yokoi, Y. Ogura, T. Noguchi, and Y. Kawarada
First Dept. of Surgery, Mie University School of Medicine, Tsu, Japan.

Few agents which exert a therapeutic effect on acute pancreatitis have been available, although various drugs such as protease inhibitors have been reported to have a prophylactic effect. IS-741, a new synthetic anti-inflammatory agent, is known to have some inhibitory effect on cytosolic phospholipase A₂ (cPLA₂), an enzyme which hydrolyzes cellular phospholipids, liberating fatty acids and lysophospholipids and providing the precursor substrates for the biosynthesis of eicosanoids and platelet-activating factor. cPLA₂ is therefore an attractive target for the development of novel therapies. The aim of the present study was to assess a therapeutic effect of IS-741 on a lethal model of acute pancreatitis in dogs, focusing on cPLA₂. **Materials and Methods.** Adult mongrel dogs were endotracheally intubated under intravenous anesthesia and maintained on spontaneously breathed room air. During infusion of lactated Ringer's solution at a rate of 10 ml/kg/hour, acute pancreatitis was induced by injecting autologous gallbladder bile into the main pancreatic duct. The dogs were then divided into two groups: Group A (non-treatment), no treatment during the experiment, and Group B (IS-741), intravenously injected with IS-741 at 6 and 30 hours after induction of acute pancreatitis. PLA₂ activity in various tissues were measured by separating the samples into high molecular fractions for cPLA₂ and low molecular fractions for secretory PLA₂ (sPLA₂) on a Sephadex column. **Results.** The survival rate was significantly higher in Group B than in Group A (80% vs. 30% at 36 hours). Mean arterial pressure, PaO₂, and creatinine clearance were well maintained in Group B as compared with Group A. The NAG index, which is known to be markedly increased in renal tubular damage, was significantly lower in Group B than in Group A. Histological examination of the pancreas, lung, and kidney in Group B showed milder changes than in Group A. cPLA₂ activity in the pancreas, lung and renal cortex was much lower in Group B than in Group A, but sPLA₂ activity in these tissues did not differ significantly between the two groups. **Conclusion.** IS-741 exerts a potentially therapeutic effect on experimental acute pancreatitis by mitigating the degree of damage in the pancreas, lung, and kidney. The inhibitory effect of IS-741 on cPLA₂ may contribute to one of the anti-inflammatory mechanism of actions of this agent.

PATHOPHYSIOLOGY OF ACUTE PANCREATITIS: ROLE OF CYTOKINES AND OTHER MEDIATORS OF INFLAMMATION. A. Salvia Department of Surgery, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston MA, USA.

Acute pancreatitis is an inflammatory disease, which varies in severity from mild to severe. Factors determining the severity of pancreatitis are not known. It is generally believed that the earliest events in the evolution of acute pancreatitis lead to premature intra-acinar cell activation of digestive zymogens and that those enzymes, once activated cause acinar cell injury. Recent studies have suggested that the ultimate severity of resulting pancreatitis may be determined by events which occur subsequent to acinar cell injury. These include inflammatory cell recruitment and activation as well as the generation and release of cytokines and other chemical mediators of inflammation.

Recently we have undertaken studies to elucidate the role of various inflammatory agents in determining the severity of pancreatitis. Results from these ongoing studies indicate that substance P acting via neurokinin-1 (NK1) receptors and intracellular adhesion molecule-1 (ICAM-1), which is expressed on the surface of endothelial cells play an important pro-inflammatory role in regulating the severity of pancreatitis. Mice that are genetically deficient in these agents have significantly less severe pancreatitis compared with the wild type mice. Furthermore, hydrolysis of platelet activating factor (PAF) by PAF-acetyl hydrolase decreases the severity of pancreatitis and associated lung injury. These results suggest that PAF plays an important pro-inflammatory role in determining the severity of this disease. On the other hand, mice deficient in complement factor 5a (C5a) receptor have more aggravated form of the disease, indicating that C5a acts as an anti-inflammatory agent during the development of pancreatitis.

NEW APPROACHES TO THE MANAGEMENT OF ACUTE PANCREATITIS

James Norman, M.D.

Division of General/Gastrointestinal Surgery, University of South Florida, USA.

A great deal has been learned during the past few years about the production of inflammatory cytokines during acute pancreatitis. At the same time, the dominant role these few mediators play in the pathogenesis of SIRS and organ dysfunction is now becoming much better understood. There is little doubt that preventing the effect of either IL-1, TNF, PAF dramatically alters the expected course of experimental pancreatitis. The question remaining is whether similar antagonism during clinical pancreatitis would benefit patients.

A major consideration is the suitability of acute pancreatitis to cytokine antagonism in the clinical setting and whether a therapeutic window exists. Although some patients present a day or two after the onset of pain, the majority seek medical attention within 12 to 18 hrs. Similarly, few patients presenting shortly after the onset of pain will exhibit organ dysfunction at that time. By the third day, however, the incidence of organ dysfunction rises rapidly to distinguish patients likely to have a protracted and complicated course. Cytokine production begins shortly after pain onset, but does not peak until 36 to 48 hrs later. If the goal is to prevent organ dysfunction, this scenario provides a therapeutic window beginning at hospital presentation and lasting two days. The results of the the first phase III anti-PAF study confirmed this theory showed dramatic beneficial effects in those treated prior to 48 hrs, but no benefit for those treated 48 hrs.

Anti-cytokine therapy in pancreatitis patients has distinct advantages over similar therapies in sepsis in that pancreatitis patients will declare the onset of their disease and therefore the initiation of the cytokine cascade. In contrast, septic patients typically declare themselves only with the onset of systemic organ dysfunction, typically after the cytokine cascade has peaked. The therapeutic window provided by pain onset during pancreatitis may allow antagonism of specific mediator while they are produced in large amounts prior to the onset of organ dysfunction. Since the majority of the morbidity and mortality of this disease is due to systemic manifestations of inflammatory mediator overproduction, acute pancreatitis is ideal suite for their antagonism.

REGULATION OF PANCREATIC MICROCIRCULATORY DERANGEMENT AND ADHESION MOLECULES IN ACUTE PANCREATITIS

M. Sunamura*, J. Yamauchi, Y. Sakai, H.M. Chen, K. Shibuya, K. Takeda, M. Kobari, S. Matsuno

1st Department of Surgery, Tohoku University School of Medicine, Sendai, Japan

Introduction: Impairment of pancreatic microcirculation in the early phase of acute pancreatitis may play a key role in the progression of this disease. In order to establish the new strategy for acute pancreatitis, we studied the increased microvascular permeability and enhanced leukocyte-endothelium interaction in acute pancreatitis.

Materials and Methods: We attained direct visualization and quantification of the change of microvascular permeability and leukocyte behavior in pancreas with acute pancreatitis using in vivo microscope system and computer analysis. Using bovine albumin fluorescein isothiocyanate (FITC) and carboxyfluorescein diacetate succinimidyl ester (CFDASE) as tracers, the change of permeability and the behavior of leukocyte in pancreatic microcirculation were quantified. Acute pancreatitis models of mice and rats were used.

Results: Bradykinin and oxygen radicals were involved in the increased vascular permeability in caerulein pancreatitis. Protease inhibitor (FOY) inhibited the increase in vascular permeability. Leukocyte adherence to the collecting venule is a secondary event following permeability changes. Expression of leukocyte integrin CD11b/18 was increased after the induction of acute pancreatitis. Cytosolic PLA₂ inhibitor (IS-741) prevents the increased expression of leukocyte integrin CD11b/18 and excessive leukocyte infiltration. Subsequently, histological findings appeared less inflammatory change in the group with IS-741. However, anti-ICAM-1 antibody did not prolong the survival period in severe acute pancreatitis model.

Conclusion: In the derangement of pancreatic microcirculation, possible contributory mechanisms include the increased vascular permeability, reduced blood flow and leukocyte-endothelial cell interaction. FOY and IS-741 are expected to play a role in regulating the pancreatic microcirculation and adhesion molecule.

A NEW APPROACH FOR THE MANAGEMENT OF ACUTE PANCREATITIS

M.H. Schoenberg, B. Rau, H.G. Beger
Department of General Surgery, University Hospital of Ulm, Ulm, Germany

Acute pancreatitis ranges from a mild self-limiting course to a severe illness with fatal outcome. The most important concept in the management of severe acute pancreatitis is early identification of those suffering from the necrotizing pancreatitis. Laboratory parameters such as C-reactive protein, lactate dehydrogenase and contrast-enhanced CT scan are highly sensitive discriminatory tests (accuracy 90%).

The initial treatment is conservative, including intensive care medicine and adequate fluid replacement. The indication for an operative intervention should be based on clinical and bacteriological data. Infection of pancreas necrosis occurs in 30 to 70%, depending on the extent of necrosis and is the key indication for the operative management of necrotizing pancreatitis. Infection of necrosis is assessed by fine-needle aspiration with a sensitivity of 77.8 and a specificity of 90.2%.

The indication for an operative intervention is persisting organ failure despite intensive care treatment and/or proven infections of pancreatic necrosis.

Necrosectomy and continuous-closed lavage of the lesser sac provide an atraumatic and tissue-sparing evacuation of debris, bacteria and toxic compounds. 140 patients who were admitted primarily to our hospital were treated accordingly. The clinical severity according to Ranson and APACHE II scores was 4.0 and 9 respectively. Intraoperative bacteriology revealed infected necrosis in 52 (37%) of patients. Lavage was carried out over medium 22 days with an initial lavage volume of 24 l/day. Postoperative complications were secondary abscess in 20%, pancreatic fistulae in 19.3%, bowel fistulae in 12.9% and systemic sepsis in 32.1%. Bleeding occurred in 15.7%. Reoperation was necessary in 36.4% (51 of 140 patients). The overall post-operative mortality of those patients who were admitted primarily to our hospital was 14.7%. This relatively low overall post-operative mortality in these patients is probably due to timely and sufficient therapy.

The novel carboxamide derivative (IS-741) attenuates lung injury in rats with cerulein-induced pancreatitis complicated by sepsis

Y. Yamaguchi, J. Liang, F. Matsumura, K. Okabe, H. Ohshiro, T. Matsuda, S. Nakano, K. Ishihara, M. Ogawa
Department of Surgery II, Kumamoto University Medical School, Kumamoto, Japan

The therapeutic effects of an intravenously injected carboxamide derivative (IS-741) on lung injury were studied in rats with cerulein-induced pancreatitis complicated by sepsis. Pancreatitis was induced by four intramuscular injections of cerulein (50 μ g/kg at 1-hour intervals). Pancreatitis rats were injected intraperitoneally with 10 mg/kg of lipopolysaccharide (LPS) 6 hours following the first cerulein injection as a septic challenge. Rats were divided into four groups: group I, pancreatitis with LPS; group II, pancreatitis with LPS treated with a continuous intravenous injection of IS-741 (0.03 mg/kg/hr); group III, pancreatitis with LPS treated with a continuous intravenous injection of IS-741 (0.3 mg/kg/hr); and group IV, pancreatitis with LPS treated with a continuous intravenous injection of IS-741 (3 mg/kg/hr). IS-741 was administered 30 minutes before the septic challenge. Intense mononuclear cell infiltration and lung hemorrhage occurred in untreated pancreatitis rats with LPS (group I), but hemorrhage was not seen in group IV rats receiving a continuous injection of IS-741 shortly before sepsis induction. The IS-741-treated rats (groups II, III, and IV) have lower serum concentrations of cytokine-induced neutrophil chemoattractant (CINC), as well as fewer the pulmonary infiltrates immunoreactive for CINC or Mac-1 (CD11b/CD18). The number of neutrophils infiltrated the lung in groups II, III, and IV was significantly lower than that of group I. Conversely, CINC production by bronchoalveolar macrophages *in vitro* were stimulated by bee venom phospholipase A2 but were reduced by the presence of IS-741. The carboxamide derivative IS-741 effectively prevented pancreatitis-associated lung injury following the septic challenge.

A NOVEL SYNTHETIC ANTI-ACUTE PANCREATITIS AGENT, IS-741

S. Yotsuya^{1,2}, H. Shikama¹, I. Nakano¹, K. Sakai¹, M. Karo¹, H. Sugi¹, H. Takada², Y. Koga²

¹Central Research Institute, Ishihara Sangyo Kaisha, LTD, Shiga, Japan.

²Research Center, Sumitomo Pharmaceuticals, Co., LTD, Osaka, Japan.

Introduction. IS-741 was first screened on the basis of PLA₂-inhibitory activity (IC₅₀: 500 μ M) and secondarily a therapeutic effect against acute pancreatitis in rats. It was shown that a therapeutic concentration in plasma (in a range of 0.1 to 0.3 μ M) was lower than the concentration of *in vitro* PLA₂ inhibition. Therefore, it was suspected that inhibition of PLA₂ did not relate to anti-pancreatic action of IS-741. It was noteworthy that IS-741 exerted an inhibitory effect on some neutrophil activity in a process of the deterioration of pancreatitis. We have studied the effects of IS-741 against some neutrophil activities in experimental acute pancreatitis.

Method. Study 1: Acute pancreatitis in rat was induced by closed duodenal loop method. IS-741 (10mg/kg) was injected intravenously at 0, 1, 2, 3, 4 and 5 hours after the induction. The number of leukocytes infiltrated into pancreas was evaluated by image analysis on the tissue sections. Study 2: Severe acute pancreatitis in rat was induced by a trypsin and taurocholic acid method. IS-741 was continuously administered for 0-24 hr by subcutaneously implanted osmotic pump. Survival rats were sacrificed for biochemical and histopathological examination at the end of administration. Study 3: *In vitro* cell adhesion of HL-60 onto HUVEC was examined.

Result. Study 1: It was shown that IS-741 had the inhibitory effect (P<0.05) on leukocytes infiltration in spleen lobe of pancreas rather than in duodenum lobe. Study 2: IS-741 (0.03 or 0.3 mg/kg/hr) suppressed the pancreatitis-associated increase in LDH, GOT, GPT, CK, HBD, BLN, Creatinine, Lipase and Interleukin-3 in serum. In histopathological examination, IS-741 improved pancreatitis associated changes, particularly on hemorrhage, neutrophils infiltration and blood vessel degeneration in various organs. Survival rates of rats receiving vehicle, 0.003, 0.03 and 0.3 mg/kg/hr of IS-741 were 20, 60, 70 (P<0.05) and 80 % (P<0.01) at 24 hr after induction, respectively. Study 3: Adherent HL-60 cells on HUVEC showed flat shape, while those treated with 1 $\times$ 10⁻⁴ M IS-741 showed spherical shape under a scanning electron microscope. The number of adherent cells was suppressed by the treatment with IS-741.

Conclusion. It has been suggested from our *in vitro* and *in vivo* studies that the inhibition of neutrophil-adhesion and/or neutrophil-infiltration into damaged organs plays an important role on the deterioration of acute pancreatitis. It is suggested that IS-741 may become a useful drug for acute pancreatitis and MOF in clinic.

POTENTIAL ROLE OF CCK IN THE DEVELOPMENT OF ACUTE PANCREATITIS - EVIDENCE FOR BENEFICIAL THERAPEUTIC EFFECTS OF CCK-A RECEPTOR ANTAGONISTS.

C. Beglinger*
Division of Gastroenterology, University Hospital, CH-4031 Basel, Switzerland

Severe acute pancreatitis results in significant morbidity and mortality. No specific therapeutic options aside supportive care have been proven to be effective in patients. The development of various animal models of acute pancreatitis (AP) has made it possible to rapidly study new approaches of potentially beneficial medical compounds. The pathogenesis of AP involves the release of lysosomal enzymes which trigger a cascade of events including activation of digestive enzymes ultimately leading to autodigestion. The initiation process of AP potentially includes activation of CCK-A receptors since blockade of these receptors with specific antagonists decreases the severity of injury in the pancreatic tissue. In the past years, a variety of potent and selective CCK-A receptor antagonists have been developed. The different antagonists have been studied in different models of AP: prophylactic administration of CCK-A receptor antagonists prevents the development of inflammation induced by cerulein or by cholin-deficient diet in rats, mice, and dogs. Along these lines of investigations, CCK-A receptor blockade ameliorated the severity of AP in bile duct- and pancreatic duct-ligated rats. This last model reflects in many ways the pathogenesis of human pancreatitis.

Conclusions. Prophylactic or therapeutic administration of CCK-A receptor antagonists ameliorates the severity of AP in different animal models; based on these observations, it was suggested that CCK-A receptor blockade with consecutive early inhibition of protease activity may be beneficial in severe AP. The results furthermore imply that endogenous CCK appears to play a contributory role in the development of AP.

MECHANISM OF CHOLECYSTOKININ (CCK)-A RECEPTOR ANTAGONIST (LOXIGLUMIDE) ON HUMAN PANCREATIC EXOCRINE SECRETION: LOCALIZATION OF CCK-A RECEPTOR IN THE HUMAN DUODENUM.

A. Funakoshi*, Y. Fukamizu, K. Miyasaka.

Department of Gastroenterology, National Kyushu Cancer Center, Fukuoka, Development Research Laboratory, Kaken Pharmaceutical Co., Ltd. Kyoto, Department of Clinical Physiology, Tokyo Metropolitan Institute of Gerontology, Tokyo.

Introduction. CCK is a physiological mediator of pancreatic enzyme secretion and gallbladder contraction through binding to CCK-A receptors. Infusion of CCK-A receptor antagonists inhibited CCK-stimulated pancreatic enzyme responses in humans. However, human pancreas predominantly expresses CCK-B receptors, whereas only CCK-A receptors were localized in the gallbladder. Thus, these data suggested that the effects of CCK on the human pancreas are mediated by CCK-A receptors, although it probably resides on neurons that may even be extrapancreatic. We tried to confirm the localization of CCK-A receptor in the human duodenum which may be another candidate of a receptor site of intestinal phase of pancreatic secretion. **Methods.** Expressions of the CCK-A and B receptor genes in human duodenum, pancreas and gallbladder were examined by the Northern analysis and RT-PCR. The autoradiographic study of CCK receptors in the duodenum was conducted in vitro and results were compared with those of the pancreas. To determine the subtypes of CCK receptors in the pancreas or duodenum, we studied the abilities of CCK-A & B receptor agonists (CCK-8 and gastrin) and antagonists (loxiglumide and L365,260) to inhibit binding of ¹²⁵I-CCK-8. **Results.** CCK-A receptor mRNA was not expressed in the pancreas, but was expressed in the gallbladder and duodenum by Northern analysis, although it was expressed in these tissues by RT-PCR. CCK-B receptor mRNA was expressed in the pancreas, but not in the duodenum. High concentrations of CCK-A receptors were detected in the duodenal mucosa by autoradiography, although in the pancreas only CCK-B receptors were detected. **Conclusion.** Localization of CCK-A receptor in human duodenum provides a biochemical and morphological basis for the some physiological functions of CCK. Inhibitory effect of CCK-A receptor antagonist on human pancreatic exocrine secretion may be indirect via neural mechanism

POSSIBLE ROLE FOR CCK FOR DEVELOPMENT AND PROGRESSION OF ACUTE PANCREATITIS (AP) AND THE THERAPEUTIC APPLICATION OF CCK RECEPTOR ANTAGONISTS. C. Niederau. Department of Medicine, Division of Gastroenterology, Hepatology and Infectious Diseases, Heinrich-Heine-University of Düsseldorf, Düsseldorf, Germany.

Introduction. This presentation reviews the role of CCK as a contributory or permissive factor for the development and progression of AP. The perspective of CCK receptor antagonists for prophylaxis and treatment of AP is discussed as well. **Methods.** The review analyzes the literature using Medline and original work. **Results.** Unequivocal evidence shows that the reduction of intraduodenal proteases results in a release of CCK thereby stimulating pancreatic exocrine secretion. Correspondingly, an acute or chronic blockade of enzyme secretion, e.g. by an impacted stone or by chronic pancreatic insufficiency causes an increase in plasma CCK. High, supraphysiological concentrations of CCK induce AP in various species including man. There is also evidence that physiological increases in plasma CCK (comparable to postprandial CCK increases) deteriorates AP in several animal models. The latter findings support the hypothesis that CCK plays a contributory or permissive role for the development of AP. The use of CCK antagonists enabled us to pursue this hypothesis. The majorities of experimental studies show that the prophylactic use of CCK antagonists ameliorates the development of AP. Most studies also show that a therapeutic application of CCK antagonists has a beneficial effect on the progression of AP. The latter effect was clearly shown for models of biliary AP in which plasma CCK is increased due to the feedback mechanism. However, there are also numerous studies which show that CCK antagonists have beneficial effects in models in which plasma CCK is not increased. It remains to be elucidated why relatively non-specific CCK antagonists, acting at the CCK-A- and -B-receptor work at least as well in AP when compared with specific CCK-A- or specific CCK-B-antagonists. The latter findings suggest that the blockade of both CCK-A- and -B (gastrin)-receptors may be more beneficial than just blocking one of the CCK-receptor types. There is also recent evidence that animal strains which do not have a CCK-A-receptor due to a genetic abnormality do not develop the same degree of AP after a certain noxious factor when compared to animals with a normal CCK-A-receptor. Further studies which recently described CCK-A- and CCK-B-receptor knockout mice allow to further study the role of CCK for the development of AP. **Conclusions.** CCK acts as a permissive or contributory factor for the development and progression of AP. There is also evidence that CCK-antagonists have a potential therapeutic benefit in AP. Thus, it is likely that clinical studies will evaluate their therapeutic potential for patients with AP.

CLINICAL EFFICACY OF LOXIGLUMIDE IN ACUTE PANCREATITIS.

H. Harada*, K. Ochi for Japan Study Group of Loxiglumide. Department of Laboratory Medicine, Okayama University Medical School, Okayama, Japan

Introduction. CCK-antagonists are promising in experimental acute pancreatitis (AP). We did a series of multicenter studies to assess efficacy and safety of Loxiglumide (Lx) in patients with AP. **Methods and Patients.** Lx was given twice daily for 14 days by a 2-h dripping venous infusion (DVI) to monitor symptoms and serum pancreatic enzymes. Adverse effects were assessed by monitoring symptoms and laboratory findings. Step-1 open trial compared efficacy between 500mg/day and 1000mg/day (30 patients each). Based on step 1, step-2 double blind trial compared efficacy between 100mg, 300mg and 500mg daily (60 patients each). Step-3 open trial assessed efficacy of Lx 500mg and Nafamostat 20mg daily (33 patients). Step-4 open trial compared efficacy between Lx 500mg/day (2-h DVI x 2) and 1000mg/day (4-h DIV x 2). **Results.** In step1, both doses showed similar efficacy (85.2% vs. 81.5%). In step2, the optimal dose was 500mg/day (Cochran-Armitage, P=0.028). In step 3, addition of Nafamostat did not alter efficacy and safety. In step 4, 1000mg/day (4-h DIV x 2) elicited a higher rate of "marked improvement." **Conclusion.** Lx 500mg/day was optimally effective in patients with AP. Dose up to 1000mg/day with a 4-h DIV seemed to enhance efficacy.

THE THERAPEUTIC EFFECTS OF CCK-ANTAGONIST ON EXPERIMENTAL ACUTE PANCREATITIS.

K. Satake¹, K. Kimura²

First Department of Surgery, Osaka City University Medical School, Osaka.¹ Development Research Lab., Kaken Pharmaceutical Ltd., Kyoto, Japan.²

Introduction. CCK is involved in the cause and the development of acute pancreatitis. The intravenous injection of CCK and its analog (caerulein) has been shown to worsen the morbidity and mortality induced by intraductal injecting rats with bile salts and by feeding a mice CDE diet. These findings suggest that CCK may play an important role in the process of development of acute pancreatitis. From these findings, many studies of CCK-antagonist in the treatment of acute pancreatitis using various experimental models found that they are effective. Most of these works, however, were conducted with caerulein-induced pancreatitis. On the other hand, it has been reported that CCK-antagonist had no beneficial effect bile- and taurocholate-induced pancreatitis. In this study, We investigated the therapeutic effects of CCK-antagonists on various models of acute pancreatitis.

Methods. Acute pancreatitis were induced by caerulein, sodium taurocholate + caerulein, and closed duodenal loop (CDL) either in mice or rats. Loxiglumide (CCK-antagonist) was used in this experiments.

Results. The intravenous injection of loxiglumide 3 and 10 mg/kg (6 times hourly intervals) significantly inhibited an increase of serum amylase levels in caerulein-induced edematous acute pancreatitis in mice, and an intravenous infusion of loxiglumide at 18 and 60 mg/kg/hr also showed remarkable improvements of the mortality rate of taurocholate-caerulein-induced necrotic acute pancreatitis in rats. Furthermore, an intravenous injection of loxiglumide showed a biochemical improvement of acute pancreatitis in rats induced by CDL. In addition, CCK-antagonist promoted from the recovery of edematous acute pancreatitis in rats induced by CDL.

Conclusion. CCK-antagonist may have a therapeutic potential on acute pancreatitis.

DIAGNOSIS OF CHRONIC PANCREATITIS AND NEWER ASPECTS OF PAIN MANAGEMENT

C.W. Imrie.

Royal Infirmary, Glasgow, UK.

The diagnosis of chronic pancreatitis in the UK largely rests on the combination of the clinical presentation which usually features pain which is often provoked by food and / or alcohol. There is usually a 30 - 40 minute delay between the stimulus and the pain and, after exclusion of other causes of pain, an ERCP is performed (+/- CT scan). A minority of patients will have pancreatic function tests carried out while increasingly the diagnosis is being made by MR scanning.

The control of pain is often the most important aspect of management to the patient. In those with large ducts due to compression of focal areas of the duct system surgical by-pass therapy is indicated. There is a bigger problem in patients with small ducts and chronic pancreatitis in whom extensive resection may be inappropriate.

Our experience with minimally invasive thoracoscopic splanchicectomy has been encouraging over the last three years. Having previously tried both percutaneous coeliac ganglion block and surgical excision of this nerve tissue, it is a great deal easier to carry out this procedure which usually takes only 15 - 20 minutes per side. Patients are usually only admitted for 48 hours and the immediate beneficial effect frequently results in opiate analgesia being discontinued with considerable improvement in quality of life. While there is a slight drop-off in benefit between six and twelve months post-operatively, the clinical effectiveness of this approach is to be commended and the author's experience will be presented to support this view.

WHAT TO DO WHEN A PATIENT WITH EXOCRINE PANCREATIC INSUFFICIENCY DOES NOT RESPOND TO PANCREATIC ENZYME SUBSTITUTION. A PRACTICAL GUIDE.

P.G. Lankisch.

Dept. of Medicine, Municipal Hospital, Lüneburg, FRG.

Background. Pancreatin microsphere preparations containing 25000 - 40000 F.I.P. units of lipase are recommended for the vast majority of patients. This will lead normally to clinical improvement and reduction of steatorrhea. However, a number of patients failing to respond present a problem for the physician in charge of their treatment.

Practical guide.

1. Increase enzyme dosage by 2 - 3 times the initial dosage. If treatment still remains unsuccessful,
2. patient compliance should be checked by asking appropriate questions or by estimating fecal chymotrypsin. If the patient is compliant,
3. the diagnosis should be reevaluated (Is it really exocrine pancreatic insufficiency?), and the doctor make tests for giardiasis, bacterial overgrowth, and blind loop in operated patients.
4. If the patient is operated (gastric section), non-acid protected granule enzyme preparations should be given. If gastroduodenal passage is disturbed (diabetes mellitus etc.) microspheres or non-acid protected granule enzyme preparations plus H₂-receptor antagonists or proton pump inhibitors should be given. If a search result is negative,
5. other intestinal absorption disorders (e.g. celiac disease) should be excluded. If this again is negative,
6. a last resort is to decrease fat intake to 40 - 60 g per day or to add H₂-blockers or proton pump inhibitors to the treatment.

Conclusion. Although this stepwise procedure is time-consuming, it is necessary to prevent in patients not responding to pancreatic enzyme substitution the development of late complications of exocrine pancreatic insufficiency.

ASSESSMENT AND TREATMENT OF EXOCRINE PANCREATIC INSUFFICIENCY

K. Kataoka, M. Hosoda, H. Yasuda, J. Sakagami, M. Kato, K. Kashima
Third Department of Internal Medicine, Kyoto Prefectural University of Medicine, Kyoto 602, Japan

Background: Enzyme replacement therapy is common in the management of patients with exocrine pancreatic insufficiency. However, lipase preparation that is acid-stable and has higher lipolytic activity is necessary to correct fat malabsorption due to exocrine pancreatic insufficiency. Furthermore, the ideal treatment should be based on reliable evaluations of exocrine pancreatic function. The secretin (S) test is the gold-standard test, but BT-PABA test or fecal chymotrypsin test (FCT) is popular in Japan. In the present study, we investigated (1) the diagnostic value of these tubeless tests in comparison to the S test, and studied (2) the *in vitro* and *in vivo* lipolytic activity of bacterial lipase (BL) that has been recently developed. **Methods and Results:** (1) The S test and the two tubeless tests were performed in 157 subjects comprising 51 patients with definite chronic pancreatitis (CP) and 27 patients with probable CP. The diagnosis of CP was based on the diagnostic criteria for CP by the Japan Pancreas Society (1995). In the S test, we analyzed fluid volume, bicarbonate concentration and amylase output of duodenal aspirates for 60 min. The results of the S test correlated with the morphological changes in pancreatic imaging tests. The values of FCT and BT-PABA test significantly correlated with max. bicarbonate concentration in the S test. The values of these tubeless tests decreased in proportion to the degree of exocrine pancreatic dysfunction. Each tubeless test was less sensitive and specific for determining exocrine pancreatic impairment than the S test. However, greater reliability for diagnosing CP can be obtained by performing the two tubeless tests simultaneously. (2) Lipolytic activities of BL and porcine pancreatic lipases (PL: Pancreatin and purified pancreatic lipase) were determined using radio-labeled triolein emulsion as a substrate. BL had a higher activity of *in vitro* lipolysis without need of colipase. In the perfusion study of double-labeled triolein emulsion into the jejunal loop in rats with bile-pancreatic juice diversion, BL had a significantly higher absorption rate of fat than PL. **Conclusion:** (1) The S test is a useful technique to evaluate exocrine pancreatic function accurately. To obtain reliable results by the tubeless test, combining BT-PABA and FCT should be performed. (2) BL may be useful in future to correct pancreatic steatorrhea.

JAPANESE PATIENTS WITH CHRONIC PANCREATITIS AND STEATORRHEA

T. Nakamura, Y. Tando, N. Yamada, T. Watanabe, K. Ogawa, A. Kaji, K. Imamura, H. Kikuchi, T. Suda

3rd Department of Internal Medicine, Hiroshima University, Japan.

Introduction. In Europe and US, steatorrhea is diagnosed so when fecal fat excretion exceeds 7 g after loading of dietary fat of 100 g. In Japan, daily fat intake is 60 g even in normal subjects with much less intake in patients with chronic pancreatitis (CP). Differences may occur between Europeans/ Americans and Japanese in frequency and severity of pancreatic steatorrhea and in therapeutic effects of pancreatic digestive enzyme therapy. The following study was conducted to elucidate characteristics of pancreatic steatorrhea in Japanese.

Patients and Methods. Sixty CP patients were divided into 2 groups; daily fat intake not exceeding 40 g (25 subjects) and exceeding 40 g (35 subjects). Consecutive 3-day feces were determined for fat by GC method. Subjects were defined as normal when daily fecal fat was not in excess of 5 g, mild steatorrhea when 5-10 g, and severe steatorrhea when exceeding 10 g. Twenty-three subjects with daily fecal fat of exceeding 5 g were treated with a pancreatic digestive enzyme preparation and the change of fecal fat excretion was examined.

Results. CP patients with dietary fat intake not exceeding 40 g revealed normal feces in 56%, mild steatorrhea in 36%, and severe steatorrhea in 8%, while those with dietary fat intake exceeding 40 g revealed 31.4%, 40%, and 28.6%, respectively. Frequency and severity of steatorrhea increased even in Japanese CP patients when dietary fat intakes were in excess of 40 g. Sufficient supplementation of the pancreatic digestive enzyme for 1 month reduced the average fecal fat excretion to 4.5 g (initial 13.9 g). Frequencies of a complete recovery, as judged so in case of not exceeding 5 g, were 17 of 23 subjects (74%).

Conclusion. Fewer frequency and less severity of steatorrhea in Japanese CP patients were ascribed to small quantity of dietary fat, and the frequency of a complete normalization of steatorrhea reached as large as 73.9%. Since the nutritional states were improved even at an average fat intake of 46.9 g, the fat intake of 40-60 g was considered appropriate for Japanese CP patients.

(a) TREATMENT OF STEATORRHOEA AFTER MAJOR PANCREATIC RESECTION CAN BE DIFFICULT, DESPITE THE USE OF HIGH DOSES OF EFFECTIVE PANCREATIC ENZYME SUPPLEMENTS.

(b) JP. Neoptolemos*, P. Ghaneh, Å. Andrén-Sandberg, S. Bramhall, R. Patankar, JH. Kleibeuker, CD. Johnson.

(c) Department of Surgery, Royal Liverpool University Hospital, 5th Floor UCD Building, Daulby Street, Liverpool, L69 3GA, UK

Introduction. Major pancreatic resection can result in steatorrhoea which is particularly difficult to control and may require high doses of pancreatin. The aim of this study was to demonstrate equivalent efficacy of high (Creon®25000) and standard dose (Creon®) pancreatin in treating steatorrhoea post-pancreatectomy. **Patients and Methods.** 42 patients, post-pancreatectomy, were assessed for a randomised, double-blind, cross-over study. Patients were stabilised on a suitable dose of Creon® during a two week run-in period. Following this they received either Creon®25000 or Creon® at this dosage for two 14 day treatment periods. Criteria used to demonstrate efficacy of treatment were stool fat excretion, stool volume, stool frequency and clinical symptoms.

Results. 39 patients were randomised and 37 completed the study. During the run-in period 22 (56%) patients had a stool fat excretion of >7g/day, with a mean capsule intake of 19.4 (range 9-54). There were significant correlations between stool fat excretion and capsule intake ($p < 0.02$), stool volume ($p < 0.0001$), stool frequency ($p < 0.01$) but not with clinical symptoms. Both Creon®25000 and Creon® demonstrated statistically similar efficacy in the treatment period.

Conclusion. The use of Creon®25000 for the treatment of pancreatic insufficiency following pancreatectomy should significantly reduce capsule intake resulting in improved convenience and compliance rate. Our results however indicate further progress is needed to resolve steatorrhoea following pancreatic resection.

MR CHOLANGIOPANCREATOGRAPHY AND VIRTUAL MR PANCREATOSCOPY: APPLICATION TO INTRADUCTAL MUCIN-PRODUCING TUMOR OF THE PANCREAS

S.Hirohashi, H.Ohishi, H.Uchida

Departments of Radiology and Oncoradiology, Nara Medical University, Kashihara, Nara, Japan

Introduction. Intraductal mucin-producing tumor of the pancreas is known as a pancreatic tumor associated with a relatively good prognosis even when the histological diagnosis is adenocarcinoma. However, once it infiltrates the pancreatic parenchyma it is known to and follow a clinical course similar to that of usual infiltrative pancreatic carcinoma, and thus its early detection is vital. The purpose of this study is to evaluate the usefulness of MR cholangiopancreatography (MRCP) and virtual MR pancreatoscopy in the diagnosis of intraductal mucin-producing tumor.

Patients and Methods. The subjects comprised 11 patients with intraductal mucin-producing tumors of the pancreas (5 main pancreatic duct type, 6 branch duct type). All the diagnosis were proven by the surgical specimen. With histopathological findings considered the gold standard the visualization of dilated main pancreatic duct, grape-like clusters, and papillary tumor of MRCP and virtual MR pancreatoscopy was compared with that of ERCP and EUS.

Results. Of the 11 cases of the intraductal mucin-producing tumor a diagnosis was possible with each of MRCP, virtual MR pancreatoscopy, ERCP and EUS in five. On MRCP and virtual MR pancreatoscopy the dilated main pancreatic duct was depicted along its entire length in all cases, whereas on ERCP because the dilated main pancreatic duct was occluded with mucin a total image could be obtained only 6 of 11 cases. With EUS an accurate diagnosis could not be made in one case with pancreatic befit. Of the 6 cases of the pancreatic duct branch duct type, on grape-like clusters could be easily grasped by both MRCP and EUS, whereas with ERCP because of the presence of the mucin total picture could not be depicted in any case, with only a part of the pancreatic duct branch visualized in 3 of 6 cases. With regard to papillary tumor present within the dilated pancreatic duct, on MRCP and virtual MR pancreatoscopy it was possible in 9 of 11 cases to point out the presence of papillary tumor as well as on EUS, whereas on ERCP because of the presence of mucin it was difficult to depict the entire pancreatic duct, and so the papillary tumor could be appreciated in only two of the 11 cases.

Conclusion. MRCP and virtual MR pancreatoscopy is important imaging modalities to diagnose intraductal mucin-producing tumor, because it can grasp non-invasively and easily the presence of tumors within the dilated pancreatic duct.

US VERSUS CT VERSUS MRI OF THE PANCREAS

Patrice M. Bret, M.D.

Radiologist in Chief Department of Medical Imaging

University of Toronto Toronto, Ontario, Canada

The current techniques used in ultrasound, CT and MRI of the pancreas will be reviewed, as well as their applications in various pancreatic diseases. Although major technical advances have recently occurred in CT (helical technology) and MRI (dynamic sequences breathhold imaging), ultrasound remains the first line examination in most of the clinical situations. Most unresectable pancreatic carcinomas can be diagnosed with ultrasound and in these situations there is no need for further investigation. Contrast-enhanced CT remains the standard for the diagnosis and follow-up of severe acute pancreatitis, although recent work shows that MRI could play a significant role in this clinical indication as it can diagnose choledocholithiasis accurately and seems to be at least as informative as contrast-enhanced CT in evaluating the pancreatic parenchyma. In islet-cell tumors, MRI has the benefit of its superior contrast resolution to detect transitory enhancement of small tumors. Finally MR cholangiopancreatography is the only non invasive method that can diagnose pancreas divisum accurately.

MR CHOLANGIOPANCREATOGRAPHY (MRCP) IN THE DIAGNOSIS OF PANCREAS DISEASES

J. Sai, J. Anyama*

Department of Gastroenterology, Juntendo University, Tokyo, Japan

Introduction. Recently, MRCP can be obtained with good spacial resolution within a few seconds using half fourier fast spin echo technique. Purpose of this study was to assess the accuracy of MRCP in the diagnosis of pancreas diseases.

Patients and Method. From July 1995 to August 1997, 1000 patients suspected of having pancreatobiliary diseases were examined with MRCP. MRCP was performed with 1.5T scanner using Fast Asymmetric Spin Echo sequence (FASE).

Results. Satisfactory quality of the main pancreatic duct were obtained in 98%, of Santorini's duct in 90%, and of uncinate process branch in 83%. Pancreas divisum was accurately diagnosed. In the patients with pancreatic ductal adenocarcinomas, MRCP depicted stenosis and proximal dilatation of the main pancreatic duct in 89%, and in the remaining patients no abnormalities were seen in the main pancreatic ducts because tumors were limited to side branches or Santorini's duct or distal end of the tail of the pancreas. Diagnosis of small pancreatic carcinomas (smallest lesion measured 10 mm in diameter) were feasible. In the patients with intraductal papillary neoplasms, dilatation of the main pancreatic duct and cystic dilatation of side branches were depicted, and polypoid lesion was detectable with source images. In the patients with serous cystadenomas, accumulation of the microcysts were visualized. In the patients with chronic pancreatitis, dilatation and stenosis of the main pancreatic duct, as well as side branch dilatation was depicted despite overestimation of the extent of the stenosis. Stones in the main pancreatic duct were well visualized as intraductal filling defects.

Conclusion. MRCP is an effective imaging technique in the diagnosis of various pancreas diseases.

DIAGNOSIS OF ANOMALOUS PANCREATICOBILIARY JUNCTION BY MEANS OF MAGNETIC RESONANCE CHOLANGIOPANCREATOGRAPHY

M. Sugiyama*, Y. Atomi, J. Hachiyu

The First Department of Surgery and Department of Radiology, Kyorin University School of Medicine, Tokyo, JAPAN

Introduction: Anomalous pancreatobiliary junction (APBJ) (a long common channel), with or without congenital choledochal cyst (CCC), is associated with a high incidence of biliary tract carcinoma. Screening for APBJ is important in patients with suspected APBJ who show a dilated bile duct, polypoid gallbladder lesions (carcinomas or adenomas) or a diffusely thickened gallbladder mucosa (hyperplasia) on ultrasonography, or acute pancreatitis of unknown etiology. ERCP depicts APBJ most reliably but is invasive and there is a potential of morbidity. Accordingly, noninvasive and accurate techniques are needed for diagnosing APBJ. We assessed the diagnostic value of magnetic resonance cholangiopancreatography (MRCP) for patients with APBJ.

Method: In 201 adult patients with pancreatobiliary disease, breath-hold (1-18 sec) MRCP was performed using a 1.5-T superconductive unit (Magnetom Vision; Siemens, Germany) and a half-Fourier acquisition single-shot turbo spin-echo (HASTE) sequence. In all patients, the length of the common channel demonstrated by MRCP was compared with that demonstrated by ERCP. In 13 patients with APBJ (the common channel ≥ 15 mm on ERCP), the diagnostic accuracy of MRCP for associated biliary diseases was evaluated.

Result: No complications were encountered in performing MRCP. On ERCP, the common channel measured 15-25 mm (mean, 19 mm) in patients with APBJ and 0-7 mm (mean, 4 mm) in those with normal junction. On MRCP, the length of the common channel was calculated to be 12-21 mm (mean, 16 mm) in 11 (85%) of 13 patients with APBJ. In the remaining two patients, the junction was not seen. In 167 (89%) of 188 patients with normal junction, MRCP identified the junction with the channel measuring 0 mm in length. MRCP failed to demonstrate the junction in the remaining 21 patients. When a 12-mm common channel length was a criterion for diagnosing APBJ by MRCP, the sensitivity and specificity were 85% and 100%, respectively. In patients with APBJ, MRCP allowed detailed visualization of CCC (all eight patients) but failed to depict carcinoma (one patient) and mucosal hyperplasia (seven patients) of the gallbladder.

Conclusion: MRCP is a noninvasive and accurate imaging method for diagnosis of APBJ and CCC. Patients with suspected APBJ should undergo further investigation utilizing MRCP.

COMPARISON OF MEDICAL AND SURGICAL THERAPY IN NECROTIZING PANCREATITIS

Edward L. Bradley, III, M.D.

Department of Surgery, State University of New York, Buffalo, USA

Randomized studies in patients with necrotizing pancreatitis which compare non-operative therapy (NOT), non-surgical alternatives such as endoscopic debridement (END) and percutaneous drainage (PCD), and standard surgical intervention (SURG) do not exist. Nevertheless, using recent advances in disease definitions, diagnostic imaging, and stratification of severity as platforms for analysis, informative comparisons can be made.

	STERILE PANCREATIC NECROSIS			INFECTED PANCREATIC NECROSIS		
	NOT*	SURG*	END*	END*	PCD*	SURG*
Number of cases	287	130	23	10	34	46
APACHE II	12.1	11.2	5.1	12.2	NS	14.6
Extent of necrosis	34%	52%	43.5%	43%	49%	61%
Organ failure	39%	56%	0%	NS	24%	62%
Intervention (Days)	N/A	8.2	48.4	46.0	NS	22.7
Efficacy	90%	92%	83%	80%	47%	87%
Overall mortality	9%	13%	0%	10%	12%	13%

NS = Not Stated, N/A = Not Applicable

Conclusions: (1) Indications for surgery in necrotizing pancreatitis continue to evolve. (2) Programmatic surgical debridement of sterile pancreatic necrosis cannot be demonstrated to improve survival. (3) Sub-groups of patients with sterile necrosis who may benefit from debridement have not as yet been characterized. (4) Cytokine antagonists such as levipitant, which have demonstrated significant reductions in mortality and morbidity in necrotizing pancreatitis can be expected to further improve results from non-operative therapy. (5) Alternatives to surgical drainage of infected necrosis deserve recognition and further evaluation.

References:

- Bradley EL III, *Pancreas*, 1996, 13, 220-223 (collected data)
- Baron TH, et al. *Gastroenterol*, 1996, 111, 755-764 (updated by personal communication)
- Freeny P, et al. *Am. J. Roentgenol* (in press)
- Bradley EL III (personal consecutive series, 1989-1997)

THE ANTIPROTEOLYTIC THERAPY FOR ACUTE PANCREATITIS

Claudio Bassi, M.D.

Surgical Department, Endocrine and Pancreatic Unit, University of Verona, Italy.

From the theoretical point of view the antiproteolytic therapy would seem to be rationale for acute pancreatitis management. Unfortunately clinical human trials studying the role of antiprotease in the treatment of acute pancreatitis differ in several respects in terms of their basic design. As a consequence any form of homogeneous analysis of the reported data as a whole is impossible.

Considering the data emerging from metaanalysis of five trials a rationale use of antiproteases may results in reduction of complications requiring surgery and of patient management costs only in selected cases, meaning by that severe and necrotic forms.

As regards presumptive applications over 400 patients were prospectively tested versus placebo in a double blind trial with the aim to prevent acute pancreatitis after ERCP. The complication incidence was significantly lower among the pre-treated patients, anyway, also in the field of protease inhibitor clinical application it is necessary to identify the patients with the greatest risk to develop post-ERCP acute pancreatitis.

In conclusion antiproteases can still play a role when prophylactically given or when in the early phases of the disease; moreover a "multiple drugs approach" (including for example suitable antibiotics) seems to represent nowadays the most modern and rational treatment of acute pancreatitis.

MANAGEMENT OF ACUTE NECROTIZING PANCREATITIS: THE ROLE OF EARLY CONTINUOUS REGIONAL ARTERIAL INFUSION OF PROTEASE INHIBITOR AND ANTIBIOTIC

Takeda K, Shibuya K, Yamauchi J, Matsuno S

First Department of Surgery, Tohoku University School of Medicine

Our strategy in the treatment of acute necrotizing pancreatitis (ANP) is as follows: Intensive medical care with continuous regional arterial infusion (CRAI) of protease inhibitor and antibiotic in the early phase, and aggressive surgical debridement for the patients diagnosed as having pancreatic infection.

Patients and methods: From 1988 to 1997, 88 patients with ANP were admitted to First Department of Surgery, Tohoku University Hospital. 67 patients admitted within seven days after the onset were treated with CRAI therapy prospectively. 22 patients received protease inhibitor Nafamostat via CRAI and antibiotic intravenously (group I) and 45 patients received both Nafamostat and Imipenem via CRAI (group II).

Results: The mortality rate in group II (13.3%) was not different from that in group I (13.7%). The incidence of infected pancreatic necrosis in group II (4.4%) was significantly lower than that in group I (22.3%). Surgical debridement was performed for pancreatic infection in eight patients in group I (36.4%) and in eight patients in group II (17.8%). None of the patients underwent surgical debridement following CRAI therapy died. The causes of death in the patients treated with CRAI therapy were related to multiple organ failure but not to pancreatic infection. The mortality rate in 17 patients received both FUT and Imipenem via CRAI within 48 hrs of the onset (0%) was significantly lower than that in 28 patients received these drugs via CRAI more than 48 hrs after the onset (21.4%).

Conclusion: Intensive medical care and early intervention with CRAI of protease inhibitor and antibiotic within 48 hrs of the onset should have a significant role in the management of acute necrotizing pancreatitis.

PROSPECTIVE STUDY OF A PROTOCOL FOR SELECTION OF TREATMENT
OF ACUTE PANCREATITIS BASED ON SCORING OF SEVERITY

H.Yokoi, T.Naganuma, T.Higashiguchi, S.Isaji, Y.Kawarada,
1st Dept. of Surg., Mie Univ. School of Medicine, Mie, Japan

Introduction. Since July 1994, we have been conducting a prospective study based on a new management protocol for acute pancreatitis.

Patients and Methods. Between July 1994 and December 1997, 50 patients with acute pancreatitis were treated according to the protocol, and their outcome was assessed in relation to etiology and severity. The protocol was based on a retrospective study of 290 cases of acute pancreatitis, including 63 cases of severe pancreatitis. The prognosis score (scoring of severity of acute pancreatitis based on the criteria of the Ministry of Health and Welfare of Japan) and APACHE II score are calculated on admission. The protocol recommends early biliary drainage for severe gallstone pancreatitis. When the prognosis score is 2 or more and the APACHE II score is 8 or more, peritoneal lavage or continuous hemofiltration plus intra-arterial infusion of protease inhibitor and antibiotics is employed. Dynamic CT studies and fine-needle aspiration of the pancreas are used to detect pancreatic necrosis and infection. When infected pancreatic necrosis is diagnosed, necrosectomy with drainage is indicated.

Results. 1) Gallstone pancreatitis : Among the 25 patients, 3 had a prognosis score of 2 or more, and 9 had an APACHE II score of 8 or more. Early biliary drainage was performed in 11 patients, and all 11 patients had a good outcome.

2) Non-gallstone pancreatitis : Among the 25 patients, the 13 with a prognosis score of less than 2 and an APACHE II score of less than 8 recovered in response to conservative treatment. In contrast, 7 of the 12 patients with a prognosis score of 2 or more or an APACHE II score of 8 or more underwent peritoneal lavage or intra-arterial infusion therapy. Five of the 7 patients were salvaged, but one died early without recovering from severe shock and the other died 4 months after the onset despite necrosectomy with drainage for infected pancreatic necrosis.

Conclusion. Our new management protocol for acute pancreatitis based on the prognosis score and the APACHE II score appears to be useful for accurately scoring severity and for selecting the method of treatment.

PART 3 General Abstracts from IAP'98 Tokyo

A SIMPLE MODEL FOR STUDYING THE MINOR PAPILLA OUTFLOW CAPACITY

T. Alempijević*, B. Štimec, M. Bulajić

Institute for Digestive Diseases, University Clinical Center; Institute for Anatomy, School of Medicine, Belgrade, Yugoslavia

The role of the minor papilla in genesis of certain pancreatic diseases has been the object of anatomical studies, particularly concerning the calibre of the accessory duct and the patency of the minor papilla. The modern improvement of endoscopic facilities and techniques (biliary manometry, EPT, stenting) call for a more profound research on minor papilla's function. In order to evaluate the outflow capacity of the minor duodenal papilla we have conducted a pilot anatomical study based on 14 fresh autopsy specimens of human duodenopancreas. The pancreases were placed in a specially modelled cradle in order to obtain a normal anatomical position and adequate hydrostatic pressures which is about 10 mmHg. After transecting the tail of pancreas, the upstream part of the major pancreatic duct and the major duodenal papilla were cannulated, and the suprapancreatic part of the common bile duct ligated. The caudal cannula was perfused with normotonic physiological solution under continuous monitoring of the pressure. After clamping the downstream cannula, we evaluated the minor papilla drainage capability. According to our model there were three types of minor papilla. Type I - patent under normal intraductal pressure. Type II - patent under increased intraductal pressure. Type III - not patent regardless of intraductal pressure. We have found papilla type I in 7 cases (50%), type II in 2 cases (14%), and type III in 5 cases (36%). Although the proposed anatomomorphological model needs some improvements, it has proven simplicity and forms basis for further studies on the accessory pancreatic drainage.

DISTAL NECROTIZING PANCREATITIS AFTER PANCREATODUODENECTOMY - SUCCESSFUL MANAGEMENT BY RADIOLOGIC INTERVENTION

H. Amano, T. Takada, M. Yoshida

First Department of Surgery, Teikyo University School of Medicine, Tokyo, Japan.

[Introduction] We experienced a necrotizing pancreatitis after pylorus preserving pancreatoduodenectomy (PPPD) in the distal side of the residual pancreas, and managed by radiologic intervention. As it seemed to be a very rare complication after PPPD, we reported about the clinical course of this case.

[Case report] A 68-year-old male admitted to our hospital complaining of jaundice. Ampullary carcinoma was suspected and PPPD with Traverso's method was performed on 26 February 1997. Pancreato-jejunostomy was made by mucosa-to-mucosa anastomosis using 5-0 Vicryl. Pancreatic parenchyma was soft and pancreatic duct was 2 mm in diameter. Amount of pancreatic juice via a pancreatic tube was about 200 ml / day and there was no evidence of pancreatic leakage. As body temperature elevated on 6 POD, CT scan was taken. Pancreatic enlargement with non-homogeneous pancreatic parenchyma in the distal pancreas and fluid collection in peripancreatic area were seen. Severity by Ranson's score and by CT findings, we assessed the condition as severe pancreatitis. Total parenteral nutrition and intensive therapies using antibiotics, H2-blocker and protease inhibitor were given, but high fever continued. Infection of pancreatic necrosis was suspected. Using radiologic intervention including CT guided puncture, drainage tubes were inserted to the appropriate places around the distal pancreas. After drainage and irrigation, pancreatic abscess disappeared gradually and the patient could discharge on 142 POD.

[Discussion] Distal necrotizing pancreatitis occurred only in one case among our 208 cases of PD and seemed to be a rare complication. Radiologic interventions were very useful in this case.

DOES OMEPRAZOLE IMPROVE EARLY GASTRIC STAGNATION AFTER PYLORUS-PRESERVING PANCREATODUODENECTOMY?

H. Amano, T. Takada, M. Yoshida.

First Department of Surgery, Teikyo University School of Medicine, Tokyo, Japan.

[Introduction] Gastric stagnation is one of the major problems after PPPD. Whether the suppressive effect of Proton Pump Inhibitor (Omeprazole) improved the gastric stasis after PPPD or not was assessed.

[Patients and Method] Forty PPPD patients were divided into two groups through a randomized enveloped controlled study. Group 1 (n=22) received Omeprazole through jejunal tube. Group 2 (n=18) were given no medications to suppress the gastric secretion and served as controls. The daily volume and total acidity of the gastric juice, aspirated via nasogastric tube, were measured 1-7 POD after PPPD.

[Results] In Group 1, the mean daily aspirated volume of gastric juice was 160.2 ml, and the mean maximum volume was 222.8 ml on 1 POD. In Group 2, six patients were withdrawn from this study due to large amount of gastric juice (exceed 2,000 ml) or gastric bleeding and received Omeprazole. The mean daily aspirated volume of gastric juice in remaining Group 2 patients was 787.4 ml, and the mean maximum volume was 1039 ml on 3 POD. Gastric secretion was significantly lower in Group 1 than in Group 2 ($p < 0.05$). The total acidity of the gastric juice was significantly lower in Group 1 than in Group 2 ($p < 0.05$).

[Conclusion] These results suggested that the administrations of Omeprazole significantly suppress the volume and acidity of the gastric juice and improved the gastric stasis after PPPD.

EFFECTIVE POST-OPERATIVE CHEMOTHERAPY ACCORDING TO THE NEW CHEMOSENSITIVITY TEST FOR ADVANCED PANCREATIC CANCER

H. Amano, T. Takada, M. Yoshida.

First Department of Surgery, Teikyo University School of Medicine, Tokyo, Japan.

[Introduction] Clinical benefit of post-operative adjuvant chemotherapy for resected pancreatic carcinoma has sometimes been unclear. Recently, we employed a new chemosensitivity test to decide the indication of post-operative chemotherapy and to choose the sensitive chemotherapeutic agents.

[Patient and Method] A 47-year-old female was diagnosed as advanced pancreatic body cancer with splenic artery and splenic vein invasion. Distal pancreatectomy with lymphadenectomy was performed on 25 November 1996. CD-DST (Collagen Gel Droplet Embedded Culture Drug Sensitivity test) was performed using the resected specimen.

[Results] 5-FU was found to be the first effective agent and CDDP, ADM and MMC were the second effective agents by CD-DST. The patient discharged after three courses of post-operative adjuvant chemotherapy using CDDP+5FU. CEA level was normal at that time. In April 1997, CEA increased to 9.1 ng / ml, four courses of CDDP+5FU and two courses of MMC+5FU were added. CEA decreased to the normal range after the chemotherapy. In August 1997, CEA increased again to 14.7 ng / ml. MMC+5FU was used in outpatient department and CEA decreased to 5.3 ng / ml in January 1998.

[Conclusion] We experienced an effective case of post-operative adjuvant chemotherapy for an advanced pancreatic cancer using sensitive drugs by chemosensitivity test (CD-DST). Chemosensitivity test seemed to be helpful for rational chemotherapy.

PANCREATIC METASTASIS FROM RENAL CELL CARCINOMA ASSOCIATED WITH PORTAL VEIN AND PANCREATIC DUCT TUMOR THROMBUS

H. Amano, T. Takada, M. Yoshida.

First Department of Surgery, Teikyo University School of Medicine, Tokyo, Japan.

[Introduction] We experienced a pancreatic metastasis from renal cell carcinoma indicating unusual spread patterns of portal vein and pancreatic duct tumor thrombus. We present radiologic and pathological findings of this case.

[Case report] A patient was 70-year-old female. She had a past history of left nephrectomy for renal cell carcinoma in February 1982. In April 1995, pancreatic head tumor was pointed out incidentally by CT, but no further examination nor treatment were done. In September 1997, She complained of a back pain. CT demonstrated the growth of the pancreatic head tumor and another tumor in the pancreatic body. Dynamic CT, MRI and angiography revealed well enhanced pancreatic tumors. Dynamic CT showed well enhanced mass in the pancreatic duct also and ERP revealed tumor thrombus in the pancreatic duct. On 22 October 1997, pylorus preserving total pancreatectomy was performed. By macroscopic findings, pancreatic tumors existed in the head and body, and tumor thrombus in the pancreatic duct and in splenic vein were found. Post operative course was uneventful and interferon therapy was applied after the operation.

[Discussion] 54 cases of pancreatic metastasis from renal cell carcinoma were reported in Japanese literature. Three cases of pancreatic duct tumor thrombus and four cases of portal vein thrombus were reported. These spread patterns seemed to be rare but characteristics of pancreatic metastasis from renal cell carcinoma.

LONG TERM (OVER TEN YEARS) RESULTS OF PANCREATOGASTROSTOMY AFTER PYLORUS PRESERVING PANCREATODUODENECTOMY

H. Amano, T. Takada, M. Yoshida

First Department of Surgery, Teikyo University School of Medicine, Tokyo, Japan.

[Purpose] Although pancreatogastrostomy has become a popular procedure after PPPD, long term results of this procedure were not clarified.

[Patients and Method] Five patients were followed over ten years after pancreatogastrostomy. Three were ampullary carcinoma and the other were pancreatic cyst and chronic pancreatitis. Post-operative changes of pancreatic duct diameter and the pancreatic functions were compared with pre-operative conditions.

[Results] In four patients, pancreatic duct diameter did not dilate by CT and US. ERP was possible in three patients with no obvious findings. In these four patients, pancreatic functions, tested by 75g OGTT and PFD test, were reserved. In one patient, pancreatic duct was gradually dilated from 2 mm to 16 mm by CT. The anastomotic site of pancreatogastrostomy was covered by gastric mucosa by gastrofiberscope. As pancreatic functions became worse and the patient complained of a back pain, re-operation was performed under the diagnosis of anastomotic obstruction. Pancreatoduodenostomy was performed on 26 March 1997. Back pain was relieved and PFD test became better from 47% to 69% three weeks after the operation.

[Conclusion] We analyzed long term results of pancreato-gastrostomy after PPPD. Pancreatic functions were reserved in patients without anastomotic stenosis. Re-anastomosis by pancreatoduodenostomy was beneficial in one patient with anastomotic stenosis.

BILIARY STONE AFTER PANCREATODUODENECTOMY-REPORT OF THREE CASES.

K. Amikura, T. Naito, M. Kobari, S. Matsuno

The First Department of Surgery, Tohoku University School of Medicine, Sendai, Japan.

Introduction. Stenosis of hepaticojejunostomy (HJ) is one of the major late complication after pancreaticoduodenectomy (PD), which may cause cholangitis or biliary stones. Three cases with biliary stone after PD were reported.

Patients. The first case is 53 years old man, who had hepatolithiasis on the hepatic hilus 7 years after PD for carcinoma of the lower bile duct. Lithotomy was performed. Seven months later, he had recurrent stone at the same site and lithotomy by percutaneous transhepatic cholangioscope (PTCS) was successfully performed. However, histological finding of the biopsy resulted in carcinoma recurrence at HJ. He died 8 months after lithotomy. The second case is 55 years old man, who had hepatolithiasis 17 years after PD for pancreatic injury caused by traffic accident. Lithotomy and dilation of HJ by PTCS was successfully performed. The Third case is 63 years old man, who had hepatolithiasis 5 years after PD for duodenal neurofibroma (von Recklinghausen's disease). Excision and reconstruction of HJ was performed. Two of 3 patients had no recurrent stone or cholangitis 4 and 1.5 years after lithotomy respectively.

Conclusion. Lithotomy and dilation of HJ by PTCS should be considered as a standard management of biliary stone after PD. The indication for the excision and reconstruction of HJ can be discussed for the inflammatory stenosis.

EARLY FAILURE OF INTESTINAL BARRIER FUNCTION AND ENDOTOXAEMIA IN SEVERE ACUTE PANCREATITIS

BJ Ammori, PG Leeder, RFG King, *GR Barclay, IG Martin, M Larvin, MJ McMahon.

Academic Department of Surgery, The General Infirmary, Leeds, UK, and *Blood Transfusion Services, The Royal Infirmary, Edinburgh, UK.

INTRODUCTION: The most life-threatening developments in acute pancreatitis are multiple organ-system failure (MOSF) and infected pancreatic necrosis. The pathogenesis of these complications remains unclear, but experimental studies suggest that translocation of bacteria and toxins via a 'leaky' intestinal mucosal barrier may contribute. The present study investigated intestinal permeability in healthy controls and patients with acute pancreatitis, its relationship with severity, and evidence for endotoxaemia.

PATIENTS & METHODS: Polyethylene glycol (PEG) 400 and PEG 3350 were selected to determine micromolecular and macromolecular intestinal permeability. PEG 400 (5g) and PEG 3350 (40g) were administered orally or via a nasogastric tube. Urinary PEG 400 and 3350 were measured by high-performance liquid chromatography. Samples were completed within 72 hours of symptom onset. Attacks were classified as mild or severe by the Atlanta Criteria. APACHE-II scores and C-reactive protein (CRP) levels were measured daily, and endotoxin and anti-endotoxin antibodies determined at admission. There were 110 subjects: 25 healthy controls; 56 mild and 29 severe attacks. Groups were matched for age and sex distribution, and mild and severe attacks for aetiology. Median admission APACHE-II was 10 (range 4-27) in severe and 5 (range 1-16) in mild attacks, median peak CRP 260 (interquartile range 156-328) mg/l in severe and 93 (interquartile range 24-163) mg/l in mild attacks.

RESULTS: Urinary recovery of PEG 400 was similar in all groups, but that of PEG 3350 was significantly greater in severe attacks (median 0.6%, interquartile range 0.26-2.2%) compared with mild attacks (median 0.09%, interquartile range 0.06-0.14%) and controls (median 0.12%, interquartile range 0.08-0.16%) (both $p < 0.0001$), as was the ratio of recovery of PEG 3350 to 400. Endotoxaemia was detected more frequently in severe compared with mild attacks (50% vs. 22%), and at greater levels (median 0.035 EU/ml vs. 0.01 EU/ml; $p = n.s.$) and was significantly higher in non-survivors than survivors (median 0.113 vs. 0.015 EU/ml; $p = 0.02$). IgG anti-endotoxin levels were significantly lower in severe compared with mild attacks (median 65.8 vs. 111 GMU, $p = 0.02$), indicating greater prior exposure to endotoxin.

CONCLUSION: Intestinal barrier function fails, and at an early stage, in patients with severe acute pancreatitis as evident by endotoxaemia and a significant increase in permeability to macromolecules. This may contribute both to the pathogenesis of MOSF, and to secondary infection of pancreatic necrosis.

Fibrogenic Cytokines Differentially Regulate Local Biosynthesis of Complement Components in the Exocrine Pancreas

A.Andoh*, H.Takaya, K.Sumiyoshi, K.Hata, M.Shimada, Y.Shintani, Y.Fujiyama and T.Bamba (Dept. of Internal Medicine, Shiga Univ. of Medical Science, Otsu, JAPAN)

Introduction. We have previously reported that complement components (C3, C4 and factor B) are locally secreted in the exocrine pancreas (*Gastroenterology* 1996;110:1919). *In vitro* data suggested that ductal epithelial cells might be local site of complement biosynthesis, and that several pro-inflammatory cytokines (IL-1 β , TNF- α and IFN- γ) participated in the regulation of this local defense mechanism. In this study, we evaluated the interaction between fibrogenic cytokines (IL-1 β , TGF- β and PDGF), which were established as mediators of pancreatic fibrosis, in the regulation of pancreatic complement (C3 and factor B) biosynthesis. **Materials and Methods.** Two pancreatic cancer cell lines, Panc-1 and MIA PaCa-2, were used. Complement levels in supernatants were determined by ELISA. Complement mRNA expression was evaluated by RT-PCR and Northern blot analysis. **Results.** The C3 and factor B synthesis was induced by the addition of one of fibrogenic cytokines, IL-1 β , in two cell lines. TNF- α also induced a marked increase in the secretion of C3 and factor B in these cells. On the other hand, the addition of TGF- β potentially attenuated the effects of both IL-1 β and TNF- α on C3 and factor B synthesis. These effects were also confirmed at the mRNA levels. The addition of PDGF also down-regulated the IL-1 β - and TNF- α -induced factor B synthesis at the protein and mRNA levels. **Conclusion.** Fibrogenic cytokines (IL-1 β , TGF- β 1, and PDGF) differentially modulated complement biosynthesis in the pancreatic cancer cell lines. IL-1 β and TNF- α induced C3 and factor B biosynthesis in these cells, but TGF- β and PDGF acted as potent down-regulators. It is likely that complement biosynthesis and fibrogenic potential in the pancreas may be closely linked by regulatory mechanisms mediated by fibrogenic cytokines.

DUODENAL HISTOLOGIC CHANGES INCLUDING ENDOCRINE CELL'S ABNORMALITIES IN CHRONIC PANCREATITIS

R.Arsić, V.Katić*, T.Tasić, I.Stamenković
Clinic of gastroenterology, Institut of pathology*, Clinical center Niš, YU

Introduction. Considering well-known anatomic and physiologic relationships between duodenum and pancreas we presumed pathohistologic changes of duodenal mucosa in chronic pancreatitis (CP).

Patients and Method. Endoscopic guided duodenal biopsies were taken from the second and the third portion in 30 patients with CP proved by means of imaging procedures (abdominal plain radiography, ERP, ultrasound and CT) and the measurement of faecal chymotrypsin.

Results. Using HE and AB-PAS technique in all cases were found different types of chronic duodenitis: DUODENITIS CHR ATROPHICA GR I in 10, DUODENITIS CHR ATROPHICA GR II in 12, DUODENITIS CHR ATROPHICA GR III in 6, and DUODENITIS CHR SUPERFICIALIS in 2 cases. PYLORIC METAPLASIA was found in 18 cases. Using specific PAP and non-specific Grimelius and Masson-Hamperi technique special attention was focused on the changes of gastrin (G-) and cholecystokinin (I-) producing cells. The all of patients had endocrine cell's abnormalities in the form of ZYMOGEN HYPOGRANULATION. Decrease in the number of G- and I-cells was found in 28 cases and had correlation with the degree of chronic atrophic duodenitis. Seven patients had the HYPERTROPHIO of G- and I-cells.

Conclusion. Patients with CP obviously have the pathologic changes of duodenal mucosa which may be consequence of CP but also may have some etopathogenetic role. DUODENITIS CHR ATROPHICA of various degree is the most frequent finding. The changes of mucosal endocrine cells, such as ZYMOGEN HYPOGRANULATION, decrease in the number or the HYPERTROPHIO of G- and I-cells may have some adaptable role in the development of exocrine pancreatic insufficiency.

STIMULATORY EFFECTS OF GOSHA-JINKI-GAN (牛車腎氣丸), A JAPANESE HERBAL MEDICINE, ON PANCREATIC EXOCRINE SECRETION IN CONSCIOUS RATS

I. Arai*, S. Amagaya, Y. Komatsu¹⁾, K. Shingu, Y. Hirai, T. Kajimoto, Y. Ida, T. Yamamoto²⁾, K. Sasaki, S. Taguchi³⁾, G. M. Green⁴⁾

¹⁾ Tsumura Kampo & Pharmacog. Labs., Ibaraki, Jpn., ²⁾ School of Pharmaceutical Sci., Showa Univ., Tokyo, Jpn., ³⁾ 2nd Dept. Int. Medicine, School of Medicine, Showa Univ., Tokyo, Jpn., ⁴⁾ Dept. Physiology, Univ. Tex. Health Sci. Ctr., San Antonio, TX, USA.

Introduction. Recently, it was reported that protease inhibitors, which stimulate pancreatic exocrine secretion by the release of CCK and secretin, delay the accelerated gastric emptying and improve postprandial hyperglycemia in diabetes by the release of CCK. Gosha-jinki-gan (TJ-107), a herbal medicine, is used for diabetes in Japan and China. In this study, we investigated the effect of TJ-107 on pancreatic exocrine secretion, and the role of CCK and secretin in its stimulative mechanism in rats.

Methods. Cannulas were inserted under anesthesia into the biliary and pancreatic duct, duodenum, stomach and jugular vein of male Wistar rats (280-320 g). Bile and pancreatic juice were returned to the duodenum continuously, and on the 3rd day, the following experiments were performed. 1) TJ-107 0.5 and 1.0 g/kg, i.g. 2) Loxiglumide, a CCK receptor antagonist, 50 mg/kg, i.g. 30 min before TJ-107. 3) In addition to loxiglumide, anti rat secretin serum 100 μ l/rat, i.v. 15 min before TJ-107. Pancreatic juice was collected every 30 min and the volume and protein output were determined. Plasma CCK was measured before, and 30 and 60 min after TJ-107 administration by RIA. Moreover, the effects of TJ-107 (0.005-50 μ g/mg) on trypsin activity was estimated by Hesterine method *in vitro*.

Results. TJ-107 stimulated the volume and protein output of pancreatic juice dose-dependently and increased plasma CCK levels. The stimulation of pancreatic exocrine secretion by TJ-107 was inhibited partly by loxiglumide and completely by anti secretin serum combined with loxiglumide. TJ-107 did not inhibit trypsin activity.

Conclusion. TJ-107 stimulated the pancreatic exocrine secretion. Its effect is considered to have been mediated by the release of CCK and secretin from the duodenum without inhibition of trypsin activity.

EXPERIENCE OF THE APPLICATION OF IMMOBILIZED POLYMYXIN B FIBER (PMX-F) IN THE TREATMENT OF SEPTIC SHOCK ON SEVERE ACUTE PANCREATITIS

Y. Asanuma, T. Furuya, S. Shibata, Y. Shindo, K. Koyama
Department of Surgery I, Akita University School of Medicine, Akita, Japan

Introduction Since 1990, the Japanese Ministry of health and Welfare has permitted the use of immobilized polymyxin B fibers (PMX-F) for the treatment of gram-negative septic shock. We have treated 9 such cases so far, and 2 out of 9 had suffered from septic shock based upon severe acute pancreatitis. Although drainage should be performed immediately after the diagnosis of infection in patients with severe acute pancreatitis, we often hesitate to do so because of the poor condition with multiple organ failure and/or septic shock status, or difficulty in diagnosing infection. The purpose of this study is to review the course of PMX-F therapy in the cases of severe acute pancreatitis. PMX-F column and direct hemoperfusion (DHP) As the PMX-F adsorbent column, Tremyxin[®] (PMX-20R) was used. Access to blood for DHP with PMX-F adsorbent therapy was obtained via a double-lumen catheter inserted into the femoral vein by Seldinger's method. DHP was carried out for 2~3 hrs at a flow rate of 100~120 ml/min. The anticoagulant was nafamostat mesilate. **Case Report** Case 1: 38 y/o male suffered from severe acute pancreatitis due to alcohol. On admission, Cullen and Grey-Turner sign were positive, APACHE II score 13, Ranson score 6 and Grade V in CT grading. Immediately after admission, protease inhibitor (Futhan) was infused continuously into splenic artery and gastroduodenal artery for 7 days, then continuous hemodiafiltration (CHDF) and respirator were initiated. On 33th day after admission he left respirator and oral intake began. However, on 57th day, he fell into septic shock, blood pressure decreased to 30 mmHg and did not increase well in spite of the dopamine administration (15 μ g/kg/min). Blood endotoxin concentration was 9214 pg/ml. PMX-F therapy was adopted once, and blood pressure became stable with less amount of dopamine (8 μ g/kg/min). After stabilization of blood pressure, CT was taken and revealed the pancreatic abscess. Immediately, celiotomy and abscess drainage was carried out. Pus Culture was MRSA positive. Postoperative course was satisfactory until 5 POD, when he passed away due to pulmonary embolism caused by the thrombus of the left common iliac vein. Case 2: 42 y/o male suffered from severe acute pancreatitis due to alcohol. On 67th day after onset, hematemesis was noted and repeated several times so that TAE of the right and left gastric artery and continuous arterial infusion of protease inhibitor were needed. On 151th day after onset, he fell into septic shock and PMX-F therapy was carried out. Endotoxin concentration decreased, and blood pressure increased immediately, then celiotomy was performed. Pancreatic pseudo-cyst existed in the bursa omentalis and penetrated the gastric posterior wall. Probably, gastric juice eroded the wall of pancreatic pseudo-cyst, subtotal gastrectomy, cholecystectomy, choledochotomy with T-tube drainage were performed. Postoperative course was uneventful. **Summary** PMX-F therapy seems to be a useful tool for secondary pancreatic infection as a bridge until the operation or for perioperative endotoxemia.

INDUCTION OF HEAT SHOCK PROTEIN AND PREVENTION OF REPERFUSION INJURY OF TRANSPLANTED PANCREAS IN RATS

Y. Asanuma, Y. Shindo, T. Furuya, S. Shibata, H. Nanjo, H. Ito*, K. Koyama
Department of Surgery I & Biochemistry II*, Akita University School of Medicine, Akita, Japan

Introduction Heat shock proteins (HSPs) are known to be involved in cytoprotection against environmental stress. We have reported the expression of HSP 60 & HSP 72 in the pancreas after whole body hyperthermia, but their protective potential has not been investigated well. The purpose of this study is to elucidate whether this response has protective effects on reperfusion injury of transplanted pancreas in rats.

Materials and Methods Induction of HSPs on donor pancreas: Under general anesthesia, Wistar male rat was pretreated with 43°C warm water-immersion for 15 min. 48 hrs later, the rat was sacrificed and pancreas was removed cautiously and preserved in 4°C UW solution for another 48 hrs. Recipient operation: Above mentioned pancreas graft was transplanted at the neck of Wistar male rat using splint technique after Nakajima. Aorta and portal vein of the pancreatic graft were connected to the jugular after and vein of the recipient, respectively. 6 hrs after revascularization, the pancreas graft was removed and evaluated as HSP group. As control group, the pancreas harvested from no pretreatment rat was used as the graft. Parameters: Pancreas weight 2. serum amylase level 3. histology 4. neutrophil infiltration in pancreas graft 5. myeloperoxidase activity (MPO) in pancreas graft

Results 1. Pancreas weight increased double in both group. 2. Serum amylase level of control group was 2463 ± 216.6 IU/l, while that of HSP group was 1784 ± 327.1 IU/l. 3. Degeneration of pancreatic graft after revascularization was clearly protected in HSP group. Followings are percentage of various histological findings comparatively show as control group / HSP group. normal acinar cell 15.9 / 58.4, vacuoles 23.7 / 3.3, necrotic change 16.6 / 1.3, edema & hemorrhage 24.4 / 2.6, edema 13.2 / 30.1, normal Langerhans' cell 61.5 / 81.5, pyknosis 3.9 / 1.0, necrosis 0.7 / 1.0, hemorrhage 25.7 / 12.4. 4. Neutrophil infiltration was 8831 ± 1987.5 / 1.5 cm^2 in control group, while it was 3420 ± 839.2 / 1.5 cm^2 in control group. 5. MPO activity was 0.655 ± 0.258 U/g of tissue in control group, while it was 0.147 ± 0.048 U/g of tissue in HSP group.

Conclusion Hyperthermia-induced HSPs gave protective potential on reperfusion injury of transplanted pancreas.

CLINICOPATHOLOGICAL STUDY OF THE PANCREATIC ENDOCRINE TUMORS

H. Baba*, M. Koike*, T. Kamisawa, N. Egawa*, A. Okamoto*
Department of Pathology*, Internal Medicine*, Surgery*, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan

Introduction. We assessed twenty eight cases of pancreatic endocrine tumors to find out if we can classify them clearly from benign to malignant.

Patients and method. Twenty eight pancreatic endocrine tumors were studied pathologically and various immunohistochemical staining was done to determine its character.

Results. By routine pathological study, 15cases(54%) were diagnosed malignant, 5cases(18%) potentially malignant, and 8cases(29%) benign. Considering the maximum tumor size, nine cases were less than 2cm and among them, one was potentially malignant, others were benign. Twelve cases were more than 4cm in maximum size and they were all malignant. We found eight cases (29%) clinically symptomatic, one glucagonoma, one somatostatinoma, six insulinomas. Ten cases were nonfunctional tumors and others were classified as asymptomatic-functional tumor, which means there is an evidence of hormonal elevation but with no clinical symptom. Eleven cases were single hormone productive tumor, seven cases were multiple. Tumor marker such as CEA or CA19-9 staining were carried out and ten cases were positive. Pancreatic secretory trypsin inhibitor (PSTI) were locally positive in nine cases and they were all diagnosed malignant by routine pathological study.

Conclusion. Pancreatic endocrine tumors are malignant when they are nonfunctional, when maximum tumor size is more than 4cm, when PSTI is found locally positive.

WHICH ETIOLOGY CAUSES THE MOST SEVERE ACUTE PANCREATITIS?

C. Assmus¹, D. Pflichthofer¹, K. Struckmann², D. Lehnick³, P. G. Lankisch¹ ¹Dept. of Medicine and ²Radiology, Municipal Hospital, Lüneburg; ³Georg-August-University, Göttingen, FRG.

Introduction. Which etiology leads to the most severe acute pancreatitis is still an open question.

Patients and Methods. This study involved 208 patients admitted with a first attack of acute pancreatitis from 1988 to 1995. The following parameters for the severity of the disease were compared within the different etiological groups: days spent in intensive care unit (ICU), total hospital stay (THS), amylase and lipase levels, Ranson, Imrie and Balthazar (contrast-enhanced computed tomography within 72 h after admission) scores, indication for artificial ventilation, dialysis or surgery, development of pancreatic pseudocysts, and mortality.

Results.

Parameters	Etiologies			
	Biliary (n=81)	Alcohol (n=69)	Other (n=16)	Unknown (n=42)
ICU (median)	5 days	5 days	3 days	6 days
THS (median)	26 days	23 days	23 days	20 days
Amylase (normal <120 U/l)	1365 U/l **	350 U/l **	476 U/l	1325 U/l
Lipase (normal <250 U/l)	7062 U/l **	1595 U/l **	1232 U/l	4550 U/l
Ranson >5 points	3 (4%)	5 (7%)	-	4 (10%)
Imrie >3 points	10 (12%)	5 (7%)	-	5 (12%)
Balthazar >4 points	10 (12%) **	20 (29%) **	2 (13%)	9 (21%)
Artificial ventilation	5 (6%)	13 (19%) **	1 (6%)	4 (10%)
Dialysis	-	1 (1%)	-	3 (7%)
Surgery	5 (6%)	11 (16%)	1 (6%)	4 (10%)
Pseudocysts	8 (10%)	19 (28%) **	2 (13%)	3 (7%)
Mortality	7 (9%)	7 (10%)	1 (6%)	4 (10%)

Biliary versus non-biliary acute pancreatitis 1+ p<0.001, 2+ p=0.034 alcohol versus non-alcohol 3+ p<0.001, 4+ p=0.026 5+ p=0.018 6+ p=0.001

Conclusion. Alcoholic etiology causes the most severe acute pancreatitis. Alcohol-induced acute pancreatitis may be either under- or overestimated on admission when only enzyme levels or CT values are considered

EXPERIENCE OF MANAGEMENT OF ACUTE PANCREATITIS WITH STILAMIN

O.Ya.Babuk, I.E. Kushnir *
Institute of Therapy of the Ukrainian Academy of Medical Sciences, Kharkov, Ukraine

Introduction. The present study was aimed on the determination of clinical efficiency and safety of Stilamin (somatostatin), conducted by the "Ares Serono" company, Switzerland, in patients with acute pancreatitis (AP).

Patients and methods. According to the protocol of multicenter Stilamin (S) trial, 5 patients were obtained: 2 men and 3 women, mean age (62 ± 8) years with the first attack of AP. S was administered within first minutes of hospitalization via continuous intravenous infusion at a rate of 250 mg/h during 5 days.

Results. After 24 to 36 hours of S infusion the pain significantly decreased and by the end of the fourth day of treatment it almost vanished. The symptoms of dyspepsia were eliminated within the first hours of S administration. During the next 24 hours in 2 patients (40%) a moderate nausea and air belching were seen. The jaundice of skin and scleras, mental disorders and seizure-like syndrome were cured in 32 hour. The wooden belly seen in 100 % of cases at the beginning of treatment, although relieved, remained in 60 % of patients till the end of the fourth day. By the middle of the fifth day of treatment it was completely relieved in 30 % of patients. The manifest leukocytosis with a shift of the leukocytic formula to the left reliably decreased after 24 hours of therapy from $11.1 \times 10^9 / l$ to $10.4 \times 10^9 / l$ and after 72 hours of continuous infusion amounted to a mean of $9.3 \times 10^9 / l$. The high blood amylase level decreased by 21% (330 U/l to 260 U/l, respectively) in as little as 72 to 96 hours after the beginning of treatment and normalized at the end treatment and lactate dehydrogenase level - from $(613 \pm 0.61) \text{ U/l}$ to $(520 \pm 8.7) \text{ U/l}$ by the end of treatment. However, it should be mentioned that after termination of S infusion the content of amylase and lactate dehydrogenase increased again in 2 patients. They were given S infusions for additional 24 hours and then switched to oral omeprazole in a dosage of 40 mg/day. There were no side effects of S.

Conclusion. The study shows a high efficiency of S in management of AP. S has an apparent inhibiting effect on the exocrine pancreatic function, mainly due to the reduction of basal and stimulated secretion of pancreatic enzymes, that accelerates resolution of inflammation in pancreatic tissue. After a continuous 120-hours S infusion antisecretory drugs in the form of tablets may be used - such as omeprazole.

PEFLOXACIN VS IMPENEM IN PREVENTING INFECTED NECROSIS: RESULTS OF A PROSPECTIVE STUDY

C. Bassi, M. Falconi, A. Bonora, R. Salvia, E. Caldiron, N. Sartori, A. Valerio, G. Butturini, C. Contro, S. Marcucci, L. Casetti, C. Dervenisi*, G. Uomo**, G. Papaccio*** and P. Pederzoli.

Department of Surgery, University of Verona, Italy

*Department of Surgery, Agia Olga Hospital Athens, Greece

**Gastroenterology Department, Cardarelli Hospital, Napoli, Italy

***Department of Surgery, Mestre-Venezia, Italy

Introduction: The treatment and prevention of infected pancreatic necrosis are a major goal in severe pancreatitis management, where antibiotic prophylaxis has recently yielded promising clinical results, with imipenem significantly reducing the incidence of infected necrosis compared to an untreated control group. Theoretically, pefloxacin's spectrum of action and pancreatic penetration should make it a valid alternative to imipenem.

Patients and Methods: In a multicentre study, 56 severe acute pancreatitis patients with necrosis affecting at least 50% of the pancreas were randomly allocated to two weeks' intravenous treatment with pefloxacin 400 mg b.d. (27 patients) or imipenem 500 mg t.i.d. (29 patients) within 120 h of onset of symptoms. Age, Sex, body weight, Ranson and Apache II scores, C reactive protein, aetiology and time from onset of symptoms to treatment were well matched in the two groups.

Results: The incidences of infected necrosis and extrapancreatic infections were 37% and 48%, respectively, in the pefloxacin group and 10.3% and 20.6% in the imipenem group, imipenem proving significantly more effective ($p < 0.05$). The mortality, due in all cases to sepsis, was not significantly different in the two groups, but was lower on imipenem (10.3% vs 18.5%).

Conclusion: Despite its theoretical potential, pefloxacin is not a valid alternative to imipenem in severe pancreatitis.

MUCIN SECRETING INTRADUCTAL NEOPLASM OF THE PANCREAS: CLINICAL EXPERIENCE ON 40 CONSECUTIVE CASES.

C. Bassi, M. Falconi, G. Zamboni*, R. Salvia, E. Caldiron, N. Sartori, C. Procacci**, A. Valerio, G. Butturini, C. Contro, S. Marcucci, L. Casetti, G. Cavallini*** and P. Pederzoli.

Department of Surgery, University of Verona, Italy

*Department of Pathology, University of Verona, Italy.

**Department of Radiology, University of Verona, Italy.

***Department of Gastroenterology, University of Verona, Italy.

Introduction: Mucin-hypersecreting intraductal neoplasms of the pancreas (TIIM) have recently been more clearly characterized on clinical, pathological and surgical grounds.

Patients and Methods: From 1985 to 1996 we observed 40 patients suffering from TIIM. All patients were submitted to preoperative assessment, consisting of routine blood examination, pancreatic markers, US and CT-scan, in 17 patients we carried out an ERCP and in 5 an US-endoscopy. Pancreatic markers showed abnormal values in 40% of cases; in 70% of cases we achieved a correct radiological diagnosis, based on enlargement of the pancreatic head without jaundice (excluding 3 patients), dilatation of the main pancreatic duct in absence of calcifications and "bulging" of the papilla of Vater.

Results: 30 patients underwent radical resective surgery, 5 patients palliative procedures, 3 cases were associated with other penampullary tumours and 2 refused total pancreatectomy and were submitted to local atypical resection. Twenty seven patients are alive and free of disease at a mean follow-up of 22.5 months (range 4-80.9), one patient after splenopancreatectomy presented with recurrence of the disease and underwent resection of the whole remaining gland.

Conclusion: The typical clinical onset of TIIM, characterized by "pancreatitis like" symptoms in the absence of risk factors for chronic pancreatitis (smoking and alcohol habit) makes the diagnosis easier; in our series we reached a correct preoperative diagnosis in about 80% of the patients.

UNDERESTIMATING ACUTE PANCREATITIS.

S. Burchard-Reckert¹, D. Lehnick², P. G. Lankisch¹. ¹Dept. of Medicine, Municipal Hospital, Lüneburg; ²Institute for Statistics and Econometrics, University of Göttingen, Göttingen, FRG.

Serum amylase and lipase measurements, along with characteristic signs and symptoms, are used worldwide to diagnose acute pancreatitis. Almost all studies on the treatment of acute pancreatitis use enzyme levels above three times the upper limit of normal ($>3n$) on admission to indicate severe disease. This assumption is questioned in this retrospective study.

Patients and Methods. 248 patients with a first attack of acute pancreatitis were divided into 2 groups according to serum amylase (group A: $\leq 3n$ = 88 patients, 31%; group B: $>3n$ = 196 patients, 69%) and lipase levels on admission (group A: $\leq 3n$ = 51 patients, 18%, group B: $>3n$ = 233 patients, 82%). Severe respiratory or renal failure (indication for artificial ventilation and/or dialysis), development of pseudocysts, indication for surgical treatment, and mortality rate were taken as parameters of severity.

Results. The results are shown in the following table:

Parameters	Serum amylase levels				Statistical significance	Serum lipase levels				Statistical significance
	Group A: ≤3n		Group B: >3n			Group A: ≤3n		Group B: >3n		
	n	%	n	%		n	%	n	%	
Renal impairment	21	23.7	99	30.1	p=0.32	15	29.4	65	27.9	p=0.86
Dialysis	2	2.3	3	1.5	p=0.65	1	1.9	9	1.7	p=1
Artificial ventilation	5	5.7	14	7.1	p=0.80	3	5.9	16	9.9	p=1
Pseudocysts	10	11.4	24	12.2	p=1	4	7.8	30	12.9	p=0.47
Surgical treatment	11	12.5	74	7.1	p=0.17	5	11.8	19	3.2	p=0.41
Mortality	4	4.5	7	3.6	p=0.74	3	5.9	3	3.4	p=0.42

Conclusion. Acute pancreatitis with serum enzyme levels $\leq 3n$ is an underestimated disease since the course of acute pancreatitis is independent of initial serum amylase levels.

Subsequent studies on the therapy of severe acute pancreatitis should use entry criteria other than serum amylase and lipase $>3n$.

SINUS TRACT ENDOSCOPY FOR RETROPERITONEAL PERI-PANCREATIC NECROSIS

R. Carter, C. McKay, C. W. Imrie

Department of Upper GI and Pancreatico-Biliary Surgery, Royal Infirmary, Glasgow, UK.

Repeated surgical exploration in patients with retroperitoneal peri-pancreatic necrosis is often associated with an initial deterioration in organ failure scores prior to subsequent improvement and carries a significant mortality. It has been postulated that the severity of this deterioration may be related to the magnitude of the surgical insult. We describe our initial experience of sinus tract endoscopy in the management of retroperitoneal peri-pancreatic sepsis.

All five patients had previously undergone formal surgical drainage with post-operative tube drainage of the retroperitoneal cavity. Recurrent sepsis was suspected by a clinical deterioration or following sequential CT, and would normally have resulted in surgical exploration. Under general anaesthesia, the previously placed tube drains were removed and where necessary the tract dilated digitally. A twin channel therapeutic gastroscope was then inserted down the tract and antegrade balloon dilatation performed as required allowing access to the abscess cavity. All visible necrotic material was then removed using endoscopic grasping forceps, brushes or snares followed by saline jet irrigation. A guide wire was placed under direct vision allowing replacement of the tube drain. All five patients recovered without further operative drainage.

Our initial results with sinus tract endoscopy in these patients is encouraging, and we are currently undertaking a more formal appraisal of the technique.

CFTR MUTATIONS AND IVS8-5T PREVALENCE IN IDIOPATHIC CHRONIC AND ACUTE RECURRENT PANCREATITIS. Castellani C*, Sgarbi D*, Cavallini G*, Di Francesco V*, Bovo P*, Frulloni L*, Vaona B*, Bonuzzato A*, Bassi C*, Falconi M*, Pederzoli P* and Mastella G* *Cystic Fibrosis Center, Ospedale Maggiore, Verona, Italy, *Gastroenterology Unit and *Surgical Dept, University of Verona, Verona, ITALY

A high frequency of mutation in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene has been detected in patients not showing the full spectrum of Cystic Fibrosis (CF) clinical manifestation, but affected by disorders that share some features with CF (i.e. congenital absence of Vas deferens, bronchiectasis, chronic obstructive pulmonary disease). An increased CFTR mutation incidence has also been recently reported in chronic pancreatitis. Aim of the study was to verify this data in a selected consecutive population of 50 patients (29 males, 21 females) suffering from chronic pancreatitis (CP) (28 pts) and acute recurrent pancreatitis (ARP) (22 pts), without any known possible etiological factor (in particular alcohol and bile stones); they had been previously classified as "idiopathic", despite in only a few of them sweat test had been performed and CF ruled out. Each subject was screened for the 15 most frequent CFTR mutations in our population: DF508, D1507, R1162X, 2183AA>G, 21303K, 3849+10KbC>T, G342X, 1717-1G>A, R553X, Q552X, G85E, 711+5G>A, 3132delTG, 2789+5G>A, W1282X), which cover 85% of CF chromosomes in our area, plus the 5-thymidine allele in intron 8 of the CFTR gene (IVS85T). Among the 28 CP patients we found 4 heterozygotes and one compound heterozygote; among the 22 ARP patients 2 heterozygotes were detected and one compound heterozygote. The two compound heterozygotes at a more thorough check up showed mild respiratory symptoms and in the CP patient the sweat electrolytes was above 100Eq/Kg. The carrier frequency was then 1:5.6 for CP and 1:7.3 for ARP, significantly higher than the expected 1/32 for tested mutations, the prevalence of IVS8-5T was instead similar to that of the general population (10%).

Even though no definitive conclusion can be drawn from our data, an impressive frequency of CFTR mutations has been detected. Some of this patients may be not just carrier but they may suffer from mild forms of CF, with CP and ARP but not major respiratory symptoms, because the presence of one known mutation on a chromosome and an undetected mutation or even a DNA variant on the other chromosome. Further studies on larger populations and/or a more extensive analysis of the CFTR gene in these subjects should be able to clarify this issue.

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ENDOTHELIN-1 IS A CANDIDATE MEDIATING INTESTINAL DYSMOTILITY IN PATIENTS WITH ACUTE PANCREATITIS

FY. Chang*, CY. Chen, RH. Lu, SD Lee.

Division of Gastroenterology, Veterans General Hospital-Taipei, Taiwan, ROC.

Introduction. Acute pancreatitis may be accompanied with gastrointestinal motor disorders. We tried to study whether gastrointestinal transit was disturbed during acute pancreatitis and to identify which mechanisms might be involved in acute pancreatitis.

Patients and Methods. Using non-invasive hydrogen breath test to measure the orocecal transit time (OCTT) represented small intestinal motility, 24 patients (M/F: 21/3, age: mean±SE, 61.5 ± 2.1 yrs) with the clinical diagnosis of acute pancreatitis were enrolled into this study. All patients received twice OCTT measurements at acute stage and recovery, respectively. Meanwhile, blood was obtained to study the amylase, lipase, C-reactive protein, erythrocyte sedimentation rate, endothelin-1 and nitrate/nitrite levels.

Results. OCTT measured at acute stage was significantly delayed compared with this at recovery (130.0 ± 9.0 vs 80.8 ± 7.4 min, p<0.001). Plasma endothelin-1 levels exhibited a positive correlation with OCTTs in acute stage (r=0.509, p=0.011). When the recovered levels were taken into consideration, the percentages of altered OCTTs also correlated with the percentages of altered plasma endothelin-1 levels (r=0.751, p<0.001). Plasma nitrate / nitrite levels significantly decreased at acute stage compared with this at recovery (5.25 ± 0.82 vs 10.20 ± 1.24 M, p<0.005), whereas their levels did not correlate with OCTTs.

Conclusion. Intestinal transit is delayed in patients with mild to moderate acute pancreatitis and symptomatic recovery is associated with normalized motility. Elevated plasma endothelin-1 levels in acute stage of these patients may be one of mechanisms mediating intestinal dysmotility.

POSSIBLE SOURCES OF BACTERIAL TRANSLOCATION TO PANCREATIC REGION: EXPERIMENTAL AND CLINICAL DATA

H. Chalkauskas, A. Pap, A. Imius, J. Bytauteme, G. Pachkauskene
Vilnius University, Clinic of Gastroenterology, LITHUANIA and
II Clinic, Gastroenterology Dept., Budapest, HUNGARY

INTRODUCTION There are well known data that the mortality rate is twice as high in infected necrotic acute pancreatitis patients comparing with non-infected. Microbiological examination shows more than 90% incidence of Gr(-) facultative enteropathogens as *Proteus*, *Enterobacter*, *Klebsiella*, *E.coli* abnormal strains, etc. Thus, colonic flora as contamination source can be expected.

PATIENTS AND METHODS We examined the microbiological status of duodenal (DC) and colonic content (CC) of chronic pancreatitis (CP) (n = 16) and functional disorders (FD) patients (n = 37). DC was collected during duodenal intubation by double lumen probe. Microbiological examination of DC and CC was performed. The ligation pancreatitis model was applied to 10 Wistar rats 5 of them got retrocecal injection of *Proteus* culture, obtained from purulent cholangitis patient.

RESULTS After 24 hours 4 of 5 infected rat were dead. Microscopical examination showed acute pancreatitis. Diffuse haemorrhagic changes in abdominal cavity were seen. The rats under the ligation pancreatitis model had usual course. *Proteus* strains are normal flora for the rat, so results can be explained by changed permeability after induction of pancreatitis and bacterial translocation, unusual pathogenic strain, from cholangitis patient bile. In the CP patients infected DC was found in 31.2% and CC 56%. In the FD patients DC was infected 14.3% and CC - 41%.

CONCLUSIONS 1. The data let us speculate that contamination of duodenum and colon by facultative pathogens could be source for bacterial translocation, as was showed in experimental pancreatitis. 2. The eradication of those infects could be prevention of severe complications in acute pancreatitis patients. 3. Clinical importance of the strains pathogenicity should be investigated.

INCIDENCE OF PANCREATIC DISEASES IN A HOSPITAL LOCATED IN CENTRAL INDIA.

Chaubey S., Jain R.C., Khatri A., Division of G.I. Surgery, Department of Medicine, St. Jude's Hospital, Sipri, JHANSI, INDIA.

OBJECTIVE - To study the incidence and pattern of pancreatic diseases in a hospital (200 Indoor capacity) located in Central India.

PATIENTS AND METHOD - A 12 month period (Jan 97 to Dec 97) was reviewed, when total of 4194 patients were admitted in the medical and surgical units of the hospital. All the clinical records of patients with pancreatic diseases were reviewed and all data regarding basic demographic, clinical, radiological and biochemical status were recorded.

RESULTS - A total of 24 (0.57%) patients with pancreatic diseases were admitted during this period. Demographic data revealed mean age 49.4 years (26 - 88 years), M:F ratio 1.1:1, 6 were smokers, 3 were Alcoholics and 2 were addicted to both. 16 were diagnosed as a case of Acute pancreatitis (11-Biliary, 2-Alcoholic, 1-trauma and 2-Idiopathic), 2 patients of pseudocyst of pancreas and 3 were of CA pancreas.

CONCLUSION - Patients of Pancreatic diseases represents a very small percentage (0.57%) in total hospital admission. Out of total pancreatic diseases patients, Acute pancreatitis due to biliary lithiasis is the most common presentation in Central India.

ENDOSCOPIC DRAINAGE OF PSEUDOCYST OF PANCREAS

Chauhe S., Vyas J.*, Division of G.I.Surgery, St.Jude's Hospital, Sipri, Jhansi, INDIA.
Sonologist, Kamala Hospital, Jhansi, INDIA.

OBJECTIVE - To evaluate the outcome of endoscopic drainage of pseudocyst of pancreas.

PATIENT AND METHOD - In a patient of pseudocyst of pancreas (Alcohol induced pancreatitis) drainage of the cyst by Endoscopic Cystogastrostomy was performed. The bulging cyst wall was punctured endoscopically under vision and the opening was enlarged resulting the drainage of cyst in the stomach.

RESULT - Follow up ultrasound done to evaluate the cyst showed complete disappearance of the cyst. There was no recurrence in follow up period.

CONCLUSION - It shows that endoscopic drainage of pseudo cyst of Panceas is an effective and simple procedure. Though it needs a larger series to confirm the results.

PROINFLAMMATORY CYTOKINES IN EARLY ASSESSMENT OF THE PROGNOSIS OF ACUTE PANCREATITIS C.C. Chen*, S.S. Wang, F.Y. Lee, R.H. Lu, S.L. Wu, F.Y. Chang, S.D. Lee. Division of Gastroenterology, Veterans General Hospital-Taipei, Taipei, Taiwan

Introduction. Proinflammatory cytokines are involved in the pathogenesis of acute pancreatitis. The value of serum levels of tumor necrosis factor alpha (TNF α), interleukin-1 beta (IL-1 β), interleukin-6 (IL-6) and interleukin-8 (IL-8) in predicting the outcome of acute pancreatitis was evaluated. **Patients and Methods.** In 50 patients with acute pancreatitis, the serum concentrations of TNF α , IL-1 β , IL-6, IL-8 and C-reactive protein (CRP) were determined on days 1, 2, 3, 4 and 7 after admission. A severe attack was defined as one that was complicated by (i) local pancreatic complications (necrosis, abscess or pseudocyst); (ii) systemic complications (acute respiratory insufficiency, renal failure, heart failure, septicemia); or (iii) death. **Results.** Serum concentrations of IL-1 β , IL-6, IL-8 and CRP on days 1 to 7 were significantly higher in patients with severe pancreatitis than in patients with mild pancreatitis. Patients with severe attacks had significantly elevated serum TNF α concentrations on days 1 to 3 compared with those with mild attacks, but not on days 4 and 7. The median peak value of TNF α , IL-1 β , IL-6 and IL-8 was reached on day 1, in contrast to the median peak of CRP, which was reached on day 2. Using cutoff levels of 12 pg/mL for TNF α , 1 pg/mL for IL-1 β , 400 pg/mL for IL-6, 100 pg/mL for IL-8 and 12 mg/dL for CRP, the accuracy rates for detecting severe pancreatitis were 72%, 82%, 88%, 74% and 80%, respectively on day 1 and 78%, 74%, 80%, 76% and 80%, respectively on day 2. Serum CRP on day 2 significantly correlated with IL-6 on days 1 and 2 ($r=0.62$ and 0.85 , respectively), but not with TNF α , IL-1 β or IL-8 on days 1 and 2. **Conclusion.** Among the proinflammatory cytokines, IL-6 is the most useful parameter for early prediction of the prognosis of acute pancreatitis.

POWER SPECTRAL ANALYSIS OF SYSTEMIC ARTERIAL BLOOD PRESSURE AND ITS CORRELATES OF THE PANCREATIC BLOOD FLOW IN CAERULEIN-INDUCED PANCREATITIS AND ENDOTOXEMIC SHOCK IN THE RAT
H.M. Chen, M.H. Shyr*, M.F. Chen. Department of Surgery and Anesthesia*, Chang Gung Memorial Hospital, Taipei, Taiwan

Introduction. We sought to evaluate the possible role of autonomic nervous system (ANS) on the cardiovascular response and regional blood flow (RBF) in the progression of acute pancreatitis and endotoxemic shock. Power spectral analysis of systemic arterial blood pressure (SAP) signals was used to evaluate the ANS functions

Materials and Methods. Acute pancreatitis was induced by intravenous infusion of caerulein (15 μ g/kg/hr) in male Sprague-Dawley rats (200-250 gm). Endotoxemic shock was induced by intravenous infusion of lipopolysaccharide (Ecoli: 0111 B4, 15 mg/kg/hr) Control animals received the same volume of normal saline. The right femoral artery was cannulated to measure SAP and subsequently its spectrum continuously. A laser doppler flowmetry (LDF) probe was attached on the pancreatic surface to measure the relative changes of capillary blood flow

Results. The activity of low and very low frequency (LF and VLF) components of SAP spectra decreased concomitantly in the early stage (1-2 hr after caerulein or lipopolysaccharide infusion) which associated with decrease of RBF in the pancreas. The activity of high and moderate frequency (HF-MF) increased. However, in both experimental conditions, total autonomic activity (VLF-LF-MF-HF) increased with parasympathetic deterioration (LF-VLF/ VLF-LF+MF-HF)

Conclusions. The deterioration of ANS function and systemic vasomotor tone were similar and correlated with microcirculatory insufficiency in the early stage of both caerulein pancreatitis and endotoxemic shock

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PRIMARY AND SECONDARY PANCREATOLITHIASIS

H-YChen, C-G Ker, T-K Yuan, C-C Juan, H-W Lo, JS Chen*, K-T Lee*, P-C Sheen*

Institute of Gastroenterology, Yuan's General Hospital, * Division of HBP Surgery, Kaohsiung Medical College Hospital. Kaohsiung, TAIWAN

Introduction. The term of primary pancreatolithiasis is the calculi located and formed in the main pancreatic duct or their branches. These stones were whitish and hard in consistency which were commonly found and reported from the literature. If the stones, especially multiple calcium bilirubinate stones from bile ductal stones migrating into the pancreatic duct called secondary pancreatolithiasis

Patients and Methods 1. Primary type There were 12 patients, male in nine and female in three. All primary type patients had a history abdominal pain for 2.5 -17 years, alcohol consumption (83.33%) and diabetes (75%). There were five (41.67%) underwent operation; lateral pancreatico-jejunostomy (Puestow procedure) in four and Whipple operation in one patients. Two patients (16.67%) were found with pancreatic cancer confirmed one during operation and another one by post-operative choledochoscopic lithotomy for removal of retained stones in the pancreatic duct 2. Secondary type There were three patients of multiple bile duct stones: two treated with sphincteroplasty and septectomy and another one treated by excision of choledochal cyst with Roux-en-Y anastomosis

Results. 1. Primary type Follow-up study revealed pain were improved in three (60%) after operation and 50% in non-operative patients treated by medicine. The diabetes condition was of non-significant improvement. Both pancreatolithiasis with pancreatic cancer were died within six months after diagnosis. 2. Secondary type All stones natures were calcium bilirubinate in nature and post-operative course was uneventful but one with retained stones

Conclusion. The pathogenesis, and stone's nature and treatment of primary and secondary pancreatic stone were absolute different. The secondary type was brown stones migrated from bile ducts especial in case of abnormal junction of pancreatic and bile ducts

HIGH CONCENTRATIONS OF INFLAMMATORY MEDIATORS IN THE PERIPANCREATIC FLUIDS IN ACUTE NECROTIZING PANCREATITIS: IS THAT AN INDICATOR OF MULTISYSTEMIC COMPLICATIONS?

F. Chikh-Torab, B. Rau, D. Berger and H.G. Beger.

Dept. of General surgery, Univ. of Ulm, 89075 Ulm, Germany.

Introduction. Significant correlations between the systemic concentrations of inflammatory mediators and severity of acute pancreatitis (AP) were demonstrated. In a prospective clinical study, we have evaluated the concentrations of inflammatory mediators in peripancreatic fluid (PF) and their relation to the development of systemic complications of AP.

Patients and methods. 19 patients (pat.) with necrotizing AP were included. The medians of Ranson and APACHE II scores were 6 (0-10) and 13 (4-22) points, respectively. Pancreatic necrosis was proved infected in 9 pat. (47.36%). Ascites and (PF) were collected through fine-needle aspiration or intraoperatively. We measured Endotoxin (etox), using LAL-Test; Tumor necrosis factor (TNF- α) and interleukin-6 (IL6), using an ELISA-technique.

Results. 1- The local concentrations of above parameters did not correlate with Ranson and APACHE II scores on the first 48 hours. 2- Only etox in PF could significantly differentiate between pat. with CT finding of pancreatic necrosis <30% of pancreatic parenchyma (7 pat., Median = 0.16 EU/ml) and pat. with pancreatic necrosis >50% (5 pat., Median = 1.5 EU/ml) ($P=0.02$). 3- Etox in PF was significantly higher in pat. who died. (11 Pat., Median = 1.5 v. 0.11 EU/ml, $P=0.006$). 4- local values of above mediators could not significantly differentiate between pat. who complicated with renal (7 pat.), or pulmonary insufficiency (17 pat.), sepsis (10 pat.) and sepsis like syndrome (7 pat.) and pat. without these complications. 5- No significant differences of concentrations of above mediators between pat. with sterile and infected necrosis. 6- Etox- and IL-6-values locally were significantly higher than their values in plasma measured on the same time [Median Etox (EU/ml): PF=1.5, Plasma=0.12, $P=0.009$, Median IL-6 (pg/ml): PF=2788, Plasma=446, $P=0.0005$]. No significant difference for TNF- α .

Conclusion. The concentration gradients of the measured parameter between plasma and PF show that the retroperitoneum represents an elective barrier, in that AP compartmentalized. The course of AP will be mainly determined with the systemic reaction, that does not correlate with the local event.

EFFECT OF REBAMIPIDE, N-ACETYL-CYSTEINE, ALLOPURINOL- AND β -CAROTENE ON CERULEIN-INDUCED ACUTE PANCREATITIS IN RAT

J.Y. Choi, K.H. Kim*

Department of Pharmacology, College of Medicine, Yonsei Univ, Seoul, Korea.

Introduction Acute pancreatitis is caused by autodigestion of pancreatic tissue induced by activated proteolytic enzyme, whose pathogenesis is not still completely understood. Recent evidence suggests that oxygen free radicals play an important role in pathogenesis of acute pancreatitis. In this experiments, we evaluated the role of oxygen radicals and the effect of small molecular weight antioxidants (rebamipide, N-acetyl-cysteine, allopurinol, β -carotene) in the development of cerulein-induced acute pancreatitis.

Methods The male rats weighting 180-200g were divided into six groups: Group I; iv infusion of a physiological saline for 3.5 hours; Group II; iv infusion of cerulein (10 μ g/kg/hr) for 3.5 hours; Group III, IV, V, VI were treated with rebamipide (100mg/kg, ip), N-acetyl-cysteine (200mg/kg, iv), allopurinol (20mg/kg/hr, concomitant with cerulein), and β -carotene (50mg/kg, ip), respectively. At the end of experiment, blood and pancreas were taken. Amylase activity in serum was assayed and pancreatic weight was measured.

As indices of oxidative stress, malondialdehyde (MDA), glutathione peroxidase (Gpx), and total glutathione (GSH) was determined. Histologic examination of the pancreas was done after H-E stain.

Results Cerulein administration resulted in significant increase in serum amylase activity and pancreatic MDA, but not Gpx. The GSH content in pancreatic tissue dramatically decreased. Pretreatment of N-acetyl-cysteine significantly decreased hyperamylasemia by cerulein and maintained GSH in pancreas but MDA was slightly decreased. Also N-acetyl-cysteine ameliorated histological damage as well. Allopurinol and β -carotene attenuated hyperamylasemia by cerulein, but histologically there was no difference from control.

Conclusion N-acetyl-cysteine is an effective antioxidant that ameliorates the hyperamylasemia and tissue damage in cerulein induced acute pancreatitis and the effect of antioxidant may need an evaluation of possible therapeutic agent against acute pancreatitis.

MUCINOUS CYSTIC TUMORS (MCT) OF THE PANCREAS: AN EXPERIENCE FROM SOUTHERN TAIWAN

Shue-Shian Chiou, Chung-Huang Kuo, Chi-Sin Changchien.

Gastroenterol. Dept., Chang-Gung Memorial Hospital, Kaohsiung, Taiwan.

Introduction. Pancreatic mucinous cystic tumors of the pancreas (MCT) are rare diseases accounting for less than 10 % of all pancreatic cysts. Despite increased clinical awareness of this entity, it continues to be confused with other pancreatic cystic tumors. Accurate diagnosis is important because of the different treatment options for benign and malignant lesions.

Patients and Method. A review was performed of all patients with a histologic diagnosis of MCT surgically treated at our hospital between 1986 and 1997. 5 cystadenoma (CYMA) and 2 cystadenocarcinoma (CYCA) were collected. The male:female ratio was 2:5 with a mean age of 51.6 years (25 to 80 years). The mean follow-up time was 2.5 years (1.5 months to 4.8 years).

Clinical Information. Site: 4 CYMA arised in the tail. The 2 CYCA and the other CYMA (3.5 cm in size) arised in the head. Size: 3.5-16 cm (mean 9.7 cm) in CYMA; 5 and 8 cm in CYCA. Symptoms: The 3 arised in the head presented with progressive jaundice. 3 CYMA arised in the tail presented with vague left upper quadrant pain and the other one presented for awareness of a mass. Associated disease: No patient was found to have diabetes mellitus or other major organ diseases. Complication: 1 CYMA complicated with splenic vein thrombosis and abscess in the tumor. Laboratory data The serum amylase was normal in the 4 CYMA checked. The serum CEA was normal in the 3 CYMA checked and mildly elevated (7.15 ng/ml) in one CYCA. On the contrary, the serum CA19-9 was normal in the 2 CYCA, but elevated in 2/3 of the CYMA. ERCP was done in 2 icteric patients (1 in each group). Both showed dilated pancreatic duct without communication with the tumors. ECHO failed to display the head tumor of the 2 icteric patients performed, but only dilated P and B ducts were shown. Cystic tumor was seen in the four tail tumors performed. CT detected all tumors but failed to make definite diagnosis preoperatively. Whipple procedure was performed for the 3 icteric patients, distal pancreatectomy for 1 and plus splenectomy for 3 CYMA. One 80 y/o CMCA died 1.5 months after operation. The others are alive till 12/97. Discussion. (1) The clinical course was usually indolent and symptoms depended more on tumor site. (2) Serum amylase, CEA and CA19-9 were of no value. (3) In contrast to ECHO, CT was an excellent tool for detection of MCT, but ineffective in distinguishing benign from malignant lesions and even pseudocyst. (4) The prognosis of benign MCT was as good as reported.

PROGNOSTIC ASSESSMENT OF ANTIPROTEASE AND INTERLEUKINS IN ACUTE PANCREATITIS

S.Chooklin*, A.Perejaslov.

Faculty Surgery Department, Medical University, Lviv, Ukraine

The presence in the blood the factors of the proteolytic enzymes inactivation are the one of the factors of the pancreas defense. α_2 -Macroglobulin and α_1 -antitrypsin are the two major antiproteases in the plasma. These antiproteases belong to the acute phase proteins II type, which induced by the IL-6 and IL-6-like cytokines. Due to this, the serum levels of α_2 -macroglobulin, α_1 -antitrypsin and IL-6 were measured in 32 patients with acute pancreatitis. Venous blood was sampled on the first, third, seventh and fourteenth days after admission. The α_2 -macroglobulin level was below the normal value in most patients, while α_1 -antitrypsin levels significantly exceeded it. The IL-6 levels were increased in all patients also. The levels of α_2 -macroglobulin, α_1 -antitrypsin and IL-6 were significantly highest in patients graded as severe (APACHE II score more than 7) compared with mild group. Maximum rise of IL-6 was noted in the first day after admission. The peak of α_1 -antitrypsin was observed on the third day after admission. Maximum decline of α_2 -macroglobulin was observed 3-7 day after admission. Due to the low levels of α_2 -macroglobulin, the inhibitory capacity of remaining α_2 -macroglobulin is decreased, what probably enables the activation of complement and kinin systems. On the favourable course of acute pancreatitis, the values of α_2 -macroglobulin and IL-6 return slowly to normal values on the fourteenth days. In patients with the fatal outcome the level of α_2 -macroglobulin was constantly low and IL-6 levels - high.

Thus, the correlation between IL-6 level and levels of α_2 -macroglobulin and α_1 -antitrypsin is the presence. The peak value of α_1 -antitrypsin and α_2 -macroglobulin lags behind the peak in serum IL-6 concentration by 48 hours.

EFFECT OF A LIQUID MEAL GIVEN AS A BOLUS INTO THE JEJUNUM STIMULATES HUMAN PANCREATIC SECRETION

L. Czakó*, F. Hajnal, J. Németh, T. Takács, J. Lonovics.

First Department of Medicine, Albert Szent-Györgyi Medical University, Szeged, Hungary

Introduction. Major features of pancreatic secretion stimulated by a meal depend on intestinal phase mechanisms. However, an intrajejunal (i.j.) meal infusion is widely used for the treatment of inflammatory pancreatic diseases, when the resting of the gland is desired. This study was undertaken to compare the effects of an intragastric (i.g.) and an i.j. complete fluid (Lundh) test meal on pancreatic enzyme secretion.

Patients and Method. Eight men (mean age: 43, range 31–48 yrs) free from pancreatic disease were studied. Pancreatic secretion was measured via a multiple lumen tube by aspiration of the duodenal juice. After a fasting period, the Lundh test meal was placed in the stomach or the upper jejunum. After the i.g. administration of the test meal, the aspirated duodenal juice was reinfused into the jejunum. The effect of atropine infusion (0.5 µg/kg/h) on the pancreatic enzyme secretion was studied. The pancreatic amylase, trypsin and lipase outputs were determined. The plasma levels of cholecystokinin (CCK) and of gastrin were measured by bioassay and radioimmunoassay, respectively.

Results. The trypsin, amylase and lipase secretions increased significantly after either an i.g. or an i.j. test meal intake. The trypsin, amylase and lipase outputs were significantly decreased during the i.j. perfusion as compared to i.g. administration (54.2 ± 6.1 , 68.7 ± 6.5 and 4.17 ± 0.3 vs 80.4 ± 13.1 , 99.4 ± 14.2 and 11.9 ± 1.2 kIU, respectively). The gastrin levels increased significantly after i.g. (20.3 ± 1.4 pg/ml), but remained unchanged after i.j. administration (16.4 ± 1.5 pg/ml). The CCK release attained its maximum 40 and 60 min following the i.g. and i.j. test meal, respectively (6.24 ± 0.7 and 4.12 ± 0.6 pM). However, the integrated CCK release was significantly lower during the i.j. administration as compared to i.g. perfusion (235.4 ± 29.1 vs 366.5 ± 32.4 pM·min). An atropine infusion significantly reduced the i.g. and i.j. test meal-stimulated enzyme outputs.

Conclusion. An i.j. administered meal stimulates the pancreatic enzyme secretion, but this effect is significantly lower than that which occurs on i.g. administration. The i.j. meal-stimulated secretion of pancreatic enzymes is subject to both cholinergic and peptidergic regulation. The deficiency of gastrin and the delayed and decreased CCK release are believed to account for the reduced enzyme output. This form of nutrient administration should not be applied in illnesses where pancreatic stimulation is undesirable.

REACTIVE OXYGEN SPECIES (ROS) ACTIVATE MAP KINASES IN PANCREATIC ACINAR CELLS

A. Dąbrowski*, C. Bogusławski, I. G. Rydzewska, A. Gabryelewicz
Gastroenterology Dept., University Medical School, Białystok, Poland.

Introduction. It has been recently reported that mitogen-activated protein kinases (MAPKs) are rapidly activated by cholecystokinin (CCK) in rat pancreas both *in vitro* and *in vivo* (Dąbrowski A. et al., *J. Biol. Chem.* 1996, 271, 5686). It is known that ROS play an important role in the pathogenesis of acute pancreatitis induced by supramaximal stimulation with CCK analogue - caerulein. The aim of our study was to evaluate whether MAPKs are activated by ROS in pancreatic acini.

Methods. The activity of both forms of MAPK, p42^{mapk} and p44^{mapk}, was determined in isolated rat pancreatic acinar cells by means of Western-blotting, with the use of highly specific antibody which recognizes active, dually phosphorylated MAPK. Acini were stimulated with different concentrations of ROS donors - hydrogen peroxide (H₂O₂), menadione (MND) or irradiated with UV-light.

Results. Incubation of acini with H₂O₂ rapidly and dose-dependently activated both forms of MAPK. Within 5 min it induced 8-fold increase of p42^{mapk} activity. At 30 min p42^{mapk} activity reached a maximum (12-fold increase), remained at a similar level until 60 min, and then significantly declined. At 120 min it was only slightly elevated (2-fold) above the control. Incubation of acini with superoxide donor - MND also induced activation of both forms of MAPK. A slight activation (1.5-fold) was observed at 5 min, and then it slowly increased reaching a maximum at 120 min, when 7-fold increase of p42^{mapk} activity was noted. The activity remained elevated (4-fold) even at 180 min. Irradiation with UV-light caused a rapid but weak increase of p42^{mapk} activity with a maximum noted at 30 min.

Conclusion. ROS strongly activate MAPKs in pancreatic acinar cells. It may be of importance in the pathogenesis of acute pancreatitis.

SURGICAL TREATMENT OF PANCREATIC NECROSIS.

J.E.M. da Cunha*, M.C.C. Machado, S. Penteado, T. Bacchella, J. Jukemura, H.W. Pinotti

Department of Gastroenterology, Surgical Division, São Paulo University Medical School, São Paulo, BRASIL

Background: Despite progress achieved in the medical treatment of patients with acute pancreatic necrosis (APN) and the role of surgery is no longer in dispute controversy still exists regarding the ideal timing of surgery.

Methods: The records of 68 patients surgically treated for APN were retrospectively reviewed to determine the influence of the time of surgery in the final outcome of the surgical treatment. Patients with pancreatic abscess and pseudocysts were excluded.

Results: The etiology of acute pancreatitis was biliary in 25, alcohol in 16 and postoperative pancreatitis in 9. Proportion of males to females was 38:1 and the average age was 46 years. The APACHE II score was calculated in all patients and it was higher than 9 in 48% (n=33).

Thirty-three patients were operated before 14 days of illness onset and 35 after the second week of onset, at the appearance of evidences of infected necrosis. The APACHE II scores for both groups were not different. The surgical procedure consisted of necrosectomy plus external drainage. Reoperation for persistent sepsis occurred in 37.8% (n=29) in the early operated patients and in 34.3% (n=12) in the delayed treated patients. Infection of the necrotic pancreatic tissue, investigated in 61 patients, was present in 33.6% (n=51), 72.5% of which were monomicrobial and was related to early laparotomy in 57% (n=29). The overall mortality rate was 26.4%. In patients with severe pancreatitis (APACHE II >9) undergoing delayed necrosectomy mortality rate was 18.7% compared to 76.5% mortality associated to early laparotomy.

Conclusion: It is concluded that necrosectomy delayed until the second week of illness onset may achieve a low mortality rate in patients with infected pancreatic necrosis.

INJECTION OF BOTULIN TOXIN INTO THE SPHINCTER OF ODDI IN PATIENTS WITH ACUTE RECURRENT PANCREATITIS: AN EFFECTIVE "MEDICAL SPHINCTEROTOMY"? V Di Francesco, L Bertolasi*, G Angelini, P Bovo, B Vaona, M Filippini, L Frulloni, T Grasso, G Talamini, N Rizzuto*, M Tebaldi and G Cavallini. Gastroenterology Unit and (*) Institute of Neurology, University of Verona, ITALY.

Sphincter of Oddi Dysfunction (SOD) has been reported as a cause of acute recurrent pancreatitis (ARP). Endoscopic or surgical division of the sphincter was able to reduce recurrences in the majority of these patients. Nevertheless pancreatic sphincterotomy may be followed by severe complications such as bleeding and necrotizing pancreatitis. Clostridium Botulinum A toxin is a potent inhibitor of the release of acetylcholine from nerve endings. Its use in esophageal achalasia has been effective in reducing lower esophageal sphincter pressure and the application in patients with sphincter of Oddi dysfunction has been suggested. Aim of this study was to evaluate the efficacy of intrasphincteric botulinum toxin injection (IBTI) in patients with ARP. Five patients (4 females, 1 male, mean age 36.4) suffering from ARP and SOD (diagnosed by the mean of a pathological US-Secretin test) entered the study. Two had prior endoscopic biliary sphincterotomy without any clinical benefit, in two cases the endoscopic attempt of dividing the papilla failed. After an informed consent was obtained patients were submitted to intrasphincteric injection of 166 U of Botulinum toxin Dysport (IPSEN) in four aliquots injected around the pancreatic sphincter via a sclerotherapy needle, passed through the operative channel of a duodenoscope. None of the patients presented pain nor enzyme elevation following the procedure and in two cases with basal pancreatic hyperenzymaemia, serum amylase and lipase dramatically fell after the treatment. The Patients were followed at 1 and 6 months after IBTI for symptoms and submitted to US-Secretin evaluation. In one case the endoscopist judged the injection too superficial (intramucosal). The same patient one month after referred a new episode of pancreatic pain and the US-Secretin still demonstrated a delayed pancreatic duct emptying. Thus the patient was treated with endoscopic sphincterotomy of both the biliary and pancreatic sphincter. In all the other 4 patients US-S was reversed to normal at 1 month follow-up. Three patients completed the first 6 months follow-up and they all reported the complete absence (two) or a substantial reduction (one) of symptoms and US-Secretin test still showed normal findings. In conclusion even if preliminary, our data show that IBTI is a safe procedure, and seems to be effective on correcting SOD in ARP patients. If longer follow-up data will confirm also an efficacy on controlling symptoms, IBTI may be proposed as a valid alternative to sphincterotomy in patients with ARP. At this stage it may be suggested for those cases with a difficult or contraindicated endoscopic approach to the papilla (i.e. difficult cannulation, minor papilla, patients with severe coagulation problems). Furthermore since the toxin as a median length of action of one year IBTI can be also suggested, as in the past endoscopic stenting, as an ex-adjunctibus temporary procedure in order to evaluate the effect of reducing pancreatic outflow obstruction.

CAN SIMPLE FECAL WEIGHT DETERMINATION REPLACE UNPOPULAR AND COSTLY FECAL FAT ESTIMATION IN THE DIAGNOSIS OF MALABSORPTION?

M. Dröge¹, H. König¹, D. Lehnrich², B. Lembcke³, P.G. Lankisch¹.
¹Dept. of Medicine, Municipal Hospital, Lüneburg; ²Georg-August-University, Göttingen; ³Johann Wolfgang v. Goethe-University, Frankfurt, FRG.

Introduction. For a diagnosis of malabsorption laboratory fecal fat estimation (van de Kamer method; J Biol Chem. 2, 347-355, 1949) is most commonly chosen. In times of low budgets it is worthwhile determining whether simple fecal weight determination can replace this unpopular and costly method.

Patients and Methods. This retrospective study includes 625 patients (319 males, 306 females). Fecal weight and fat estimation were performed in stools collected for 72 hours during the course of diagnosis of malabsorption.

Results. The results are presented in the following table:

Fecal fat	Fecal weight		All
	≤200 g/d	>200 g/d	
>7 g/d	97 (15.5%)	139 (22.2%)	236 (37.8%)
≤7g/d	336 (53.8%)	53 (8.5%)	389 (62.2%)
All	433 (69.3%)	192 (30.7%)	625 (100%)

The correlation between both methods was significant: $r=0.68$; $p<0.001$; Spearman's correlation coefficient, however, yielded divergent results in 150 (24%) of 625 patients.

If only fecal weight were used as sole indicator of raised fecal fat, 53 (27.6%) of 192 patients would have been wrongly classified as having steatorrhea (false positive results) and steatorrhea in another 97 (22.4%) of 433 patients with normal fecal weight would have been overlooked (false negative results).

Conclusion. Fecal weight estimation for the diagnosis of malabsorption is not reliable enough to replace the van de Kamer method for the diagnosis of steatorrhea.

CHALLENGING SURGICAL DOGMA: Nasogastric feeding in severe acute pancreatitis may be practical and safe.

F. C. Eatock, G. D. Brombacher, A. Steven, C. W. Imrie, C. R. Carter.

Department of Upper GI and Pancreatico-Biliary Surgery, Royal Infirmary, Glasgow, UK.

Severe acute pancreatitis may be protracted and some form of nutritional support is frequently required to maintain the patient's status. Recent work has suggested that enteral feeding may reduce the magnitude of the inflammatory response. Insertion of nasojejunal tubes in the patient with severe acute pancreatitis carries procedure-associated risks and involves both delay and inconvenience. Therefore, we undertook a Phase I study to assess the safety of nasogastric feeding in patients with severe acute pancreatitis.

27 patients admitted to our unit with severe pancreatitis received nasogastric feeding within 48 hours. Aetiology was identified as cholelithiasis (20 patients), ethanol (5) and miscellaneous (2). The median Glasgow score was 3 (range 1-7), APACHE II score 8 (1-28) and C-reactive protein concentration 195.5 mg/l (79-385). Seventeen patients had pancreatic and/or peripancreatic necrosis. Nineteen patients underwent ERCP, five necrosectomy for infected necrosis, and three patients internal drainage of a pseudocyst. Ventilatory support was necessary in nine patients, five of whom also required inotropic support with two also having renal dialysis. There were three deaths (11.1%).

The feed was well tolerated in all but three patients. There was no evidence of clinical or biochemical deterioration on commencing nasogastric feeding. It would appear that early nasogastric feeding in severe acute pancreatitis is safe, well tolerated and worthy of further study.

LOCAL DELIVERY OF IL-12 INDUCES ANTI-ANGIOGENESIS EFFECT IN PANCREATIC CANCER

D. G. Duda, M. Sunamura*, R. Son, G. Matsumoto, L. Lozonchi, L. Ding, M. Kobari, S. Matsuno
 First Department of Surgery, Tohoku University Medical School, Sendai, Japan

Introduction. Interleukin 12 (IL-12) was proved to induce a potent antitumor and antimetastasis immune response in different models. It has been also reported that IL-12 possesses anti-angiogenesis effect. The aim of this study is to clarify the anti-angiogenesis effect of IL-12 on human pancreatic carcinoma using a vital microscope system. Furthermore, we investigated the efficacy of IL-12 local delivery system using genetically engineered fibroblasts.

Materials and Methods. We used severe combined immune-deficient mice (SCID). Skinfold Chamber models was used to evaluate tumor growth and angiogenesis after implantation of PK-1 (pancreatic carcinoma cells) or IL-12 genetically engineered PK-1 (IL-12/PK-1). Local and systemic levels of IL-12 and IFN gamma were measured by ELISA. Images of neovascularization were recorded through intravital microscopy and analyzed off-line. The effects of anti-IFN gamma and anti-IL-12 antibodies were investigated. Anti-asialo GM1 antibody was injected to block the natural immunity. We implanted PK-1 with either wild type fibroblasts (NIH/3T3) or IL-12 transfected fibroblasts (IL-12/3T3) and compared in vivo tumor growth. Immunohistochemistry was performed.

Results. Although there was no difference in growth curve in vitro between PK-1 and IL-12/PK-1, the growth of IL-12/PK-1 was inhibited significantly as compared with PK-1 in vivo. Skinfold chamber studies showed a strong inhibition on tumor angiogenesis of IL-12/PK-1. IL-12 antibodies administration allowed tumor development after IL-12/PK-1 implantation. Tumor growth of PK-1 was also prevented by co-inoculation with IL-12/3T3. No side effect was observed.

Conclusion. It is demonstrated that anti-angiogenesis effect of IL-12 prevented the growth of pancreatic cancer. Local delivery system of IL-12 is expected to be a new strategy for pancreatic cancer.

ANTI-ANGIOGENIC TREATMENT ON PANCREATIC CANCER

S. Egawa*, L. Lozonchi, D. Duda, M. Akada, H. Inoue, M. Kosaka, M. Onuma, S. Fukuyama, M. Sunamura, M. Kobari, and S. Matsuno

First Department of Surgery, Tohoku University School of Medicine, Sendai, Japan.

Introduction The extremely poor prognosis of pancreatic cancer urges us to develop a new modality of treatment for this disease. Recently, angiogenesis has been proved to play a crucial role in the growth, invasion and metastasis of various kinds of tumors. In this study, the angiogenic properties of eleven human and one Syrian hamster pancreatic cancer cell lines were analyzed and experimental anti-angiogenic therapeutics were adopted *in vivo*. **Methods / Results.** The conditioned media of these cell lines promoted the proliferation of endothelial cells *in vitro*. Northern blot and RT-PCR analyses revealed that all twelve pancreatic cancer cell line express vascular endothelial growth factor (VEGF) and with a high frequency of overexpression (7 out of 12) without any hypoxic conditions. The hamster pancreatic cancer cells also expressed acidic fibroblast growth factor, transforming growth factor- β and an excess amount of transforming growth factor- α . TNP-470, one of the first generation anti-angiogenic agent, inhibited the growth of syngeneic subcutaneous tumors of the hamster cell line although it did not have a direct cytotoxic effect in vitro. The histological sections of the tumors revealed that the amount of interstitial tissue and vessel densities ($p<0.05$ vs control) of the treatment group were significantly decreased with deteriorated cancer cell viabilities. **Conclusion.** These data suggest that angiogenesis plays an important roles in the tumor growth of pancreatic cancer and the anti-angiogenic treatment can be a new powerful medical treatment modalities against this fatal disease.

EFFECTS OF A COMBINATION OF RETINOIC ACID AND INTERFERON γ ON HUMAN PANCREATIC CARCINOMA CELLS IN VITRO

N. Egawa^{*1}, Y. Tu¹, T. Morohoshi².

Dept. of Internal Medicine, Tokyo Metropolitan Komagome Hospital¹, 1st Dept. of Pathology, Showa University², Tokyo, Japan.

Introduction. The combination therapy of all-*trans*-retinoic acid (ATRA) and Interferon γ (IFN γ) inhibits growth in some cell lines. In pancreatic cancer cells, this effect has not been investigated so far.

Methods. Three established human pancreatic ductal adenocarcinoma cell lines, PT45, Colo 357 and A818-1, were used. They were treated with ATRA (1 μ M), IFN γ (5U/ml) and the combination of these two agents. After the continuous treatment for four days, changes of cell growth, morphology and immunocytochemistry (CEA, CA19-9, p53, Bcl-2 and Ki-67) were studied. Detection of apoptosis was also carried out at day 4.

Results. Cell growth was inhibited in all three cell lines followed in order by the combination treatment, IFN γ and ATRA. Synergistic effect was seen only in A818-1. Morphological changes were found in all cell lines, especially after the treatment with IFN γ and the combination. They included increases of microvilli or mitochondria. Colo 357 showed increasing Ki-67 labeling index after each treatment. However, the other cell lines did not reveal any changes of immunocytochemistry. Apoptosis was detected in all the cell lines. Despite possessing mutant p53, PT45 disclosed prominent apoptosis. This indicates the existence of p53-unrelated apoptosis in the pancreas cancer cell lines.

Conclusion. The combination therapy of ATRA and IFN γ may be an effective strategy for pancreatic carcinoma.

THREE-DIMENSIONAL STRUCTURE OF THE PANCREATIC DUCTULE AND THE INTRA-ACINAR SECRETORY CANALICULUS

H. Endoh, N. Ashizawa*, N. Hamamoto, Y. Kinoshita.

Dept. of Internal Medicine II, Shimane Medical University, Izumo, Japan.

Introduction. On the basis of light-microscopic reconstruction of pancreatic tissue, Bockman reported that the ductules and acini were arranged in a complex, branching system of tubules, which anastomose and end blindly, whereas Takahashi claimed that there was no anastomosis among the intercalated ducts and acini. However, it is impossible to recognize the three-dimensional structure of the intra-acinar secretory canaliculus and the peripheral intercalated duct by light microscopy, since their lumina are less than 1 μ m in diameter.

Method. The common hepatic duct of the rat was ligated proximal to its entry into the pancreas, and the common bile-pancreatic duct was also ligated near its junction with the duodenum. A specimen of pancreatic tissue taken one day after ligation was fixed in buffered 10% formaldehyde solution, embedded in styrene, and serial sections 0.5 μ m thick were cut and observed by scanning electron microscopy (a new method devised by Naora). The intra-acinar secretory canaliculi and the peripheral intercalated ducts in each section were then reconstructed.

Results. In some acini, two intra-acinar secretory canaliculi joined a canaliculus, which ended blindly. A few non-branched intercalated ducts interconnected two adjacent intra-acinar secretory canaliculi. However, all the intra-acinar secretory canaliculi ended blindly close to the basement membrane.

Conclusion. The intercalated ducts and the intra-acinar secretory canaliculi are arranged in a complex branching system, but the latter, which are the most peripheral pancreatic ducts, end blindly.

CLINICAL CHARACTERISTICS OF PANCREATIC CARCINOMA PRECEDED BY DIABETES MELLITUS

N. Egawa^{*1}, Y. Tu¹, T. Kamisawa¹, J. Ishiwata¹, K. Tsuruta², A. Okamoto², M. Koike³.

Dept. of Internal Medicine¹, Dept. of Surgery², Dept. of Pathology³, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan.

Introduction. There is a close relationship between pancreatic carcinoma and diabetes mellitus (DM). However, it is still controversial if DM is a true risk factor of pancreatic cancer or not.

Patients and Method. We reviewed 322 patients with pancreatic cancer who were admitted to our hospital between 1975 and 1994. Of these patients, 26 (16 males and 10 females) had suffered from DM for 2 years or more before the diagnosis of the pancreatic cancer (Group A). We studied their clinical data comparing with the rest of the patients as a control (Group B).

Results. Group A consisted of 13 head and 13 body and/or tail carcinoma. Group B had 168 and 128, respectively. There was no difference in initial symptoms between two groups. In 3 patients of Group A, DM control had deteriorated before the diagnosis of pancreatic cancer. Family history of DM was seen in 33% of Group A and 13% of Group B ($p < 0.05$). Histology other than tubular adenocarcinoma was found in 50% of Group A and 12% of Group B. Fifteen % of Group A survived for 2 years or more after the initial symptoms, while 7.5% in Group B.

Conclusion. It was not clear that DM is a true risk factor of pancreas carcinoma. However, it is noteworthy that Group A included uncommon cancers compared to Group B. Periodic checkup on DM patients is worthwhile for picking up pancreas cancer.

CAN KI-67 ANTIGEN EXPRESSION PREDICT THE OUTCOME OF PANCREATIC CANCER ?

C. Ferrara, *A. Poletti, G. Tesson, T. Meggiato, **A. Corsini, G. Del Favero, D. Depts of Gastroenterology, * Pathology & ** Surgery II - Università degli Studi - Padova - ITALY -

Introduction Ki-67 antigen allows to determine the proportion of proliferating tumour cells and it is a useful prognostic indicator for several tumours such as lung, breast carcinoma, NK lymphomas and melanoma. The aims of our study were to evaluate 1. the expression of this antigen in pancreatic cancer; 2. the correlation of Ki-67 expression with the histological features of the tumour and the outcome of patients. **Patients and Methods.** The surgical specimens of ductal pancreatic carcinoma were collected from 14 patients who underwent to radical surgery. In three of them the lymph nodal metastases were also evaluated. 8 biopsy were obtained from liver metastases in subjects submitted to palliation. 5 specimens of normal pancreas were obtained from organs donors (control group). Ki-67 antigen was determined in pancreatic tissue by immunohistochemistry (MIB 1, DBA Italia) and expressed as percentage of positively stained nuclei/total number of nuclei counted. Ki-67 antigen was related to patients survival (< 12 months=short-term survivors and >12 months=long-term survivors), stage, architectural and cytological grading and vascular, lymph node, perineural invasion by Student's t test for unpaired data and linear regression. **Results.** Antibody binding was only rarely (<5%) observed in the nuclei of normal pancreas. The percentage of pancreatic cancer positive cells showed a mean value of 12.8% in primary tumour. In 2 lymph nodes the percentage of cellular nuclei stained was higher than in the corresponding primary tumour, whereas the percentage was similar in the third case. All liver metastases were positive for Ki-67 expression. The Ki-67 staining in pancreatic cancer tissue (mean 12.8%) was lower than in the metastases (mean 32.5%) ($p=0.02$). Significantly lower values were found in long-term survivors (3.8%) as compared to the short-term survivors (18.1%) ($p=0.008$). The expression of Ki-67 was not correlated with architectural and cytological grading. A positive relation was demonstrated between the expression of this antigen and stage ($p<0.05$), lymph node state ($p=0.04$) node perineural invasion ($p=0.0001$). **Conclusions.** 1. Ki-67 antigen is overexpressed in pancreatic cancer cells. 2. the patients with higher expression of Ki-67 antigen have a poor prognosis. 3. The elevation of Ki 67 antigen in addition to histological features of pancreatic carcinoma is useful in predicting patient outcome.

A) THE EORTC QLQ-PAN26 A MULTILINGUAL APPROACH TO THE ASSESSMENT OF QUALITY OF LIFE IN INTERNATIONAL PANCREATIC CANCER CLINICAL TRIALS

B) D Fitzsimmons*, S George, S Payne, CD Johnson et al on behalf of the EQoLIPa study group

C) Pancreatic and Biliary Research Group, University of Southampton, Southampton, United Kingdom.

Introduction: Quality of life (QoL) assessment is now a mandatory endpoint of cancer clinical trials, yet no pancreatic cancer specific QoL questionnaire exists. We report on the development of the European Organisation for Research and Treatment of Cancer (EORTC) pancreatic cancer QoL module to supplement the core cancer module the QLQ-C30. **Patients and Methods.** The EORTC guidelines for module development were followed. Phase 1 (generation of relevant issues) involved extensive literature searches, and qualitative interviews with 6 specialists and 34 patients in the UK. Phase 2 involved construction of a questionnaire, peer review by international specialists and EORTC and translation using a forwards backwards technique into 12 European Languages. Phase 3 (pretesting) involved administration of the QLQ-C30, a provisional pancreatic cancer module and a qualitative debriefing interview. This was performed in 78 patients across 8 countries, stratified into 4 groups by disease stage and treatment intention.

Results: Phase 1 identified over 80 issues, of which 42 were specific issues for pancreatic cancer patients. Phase 2 resulted in the construction of a provisional 26 item module. Pretesting identified that 22/26 questions had an adequate range of responses, mean value and prevalence >30. 4/6 multi item scales have adequate internal reliability (Cronbach's alpha >0.7) and construct validity (Spearman's r 0.4-0.6). The median time of completion was 12 mins. Qualitative analysis indicates that the module is easy to complete and cross culturally applicable. Two additional items were identified, sexuality and bowel habit, resulting in a final 26 item module.

Conclusion: The QLQ-PAN26 is a valid, reliable and cross culturally applicable instrument for the assessment of quality of life in patients undergoing international clinical trials for pancreatic cancer.

HIGH SERUM LEVELS OF SECRETORY IMMUNOGLOBULIN A (sIgA) IN ADVANCED CHRONIC PANCREATITIS (CP).

L. Frulloni, *M.Negri, *M.Zanini, P. Bovo, S. Brunelli, V. Di Francesco, B. Vaona, M. Filippini, M.P. Brunon, P.C. Farris, B. Calore and G. Cavallini. *Cattedra di Gastroenterologia, University of Verona. e *Laboratorio Chim. Clin. and Ematol. Ospedale Maggiore Verona, Italy.*

Background: Elevated levels of sIgA have been reported in patients with cholestatic hepatitis and correlate with hepatic fibrosis in HCV chronic hepatitis patients. sIgA are present in the biliary and pancreatic tract. CP is a disease characterized by patchy and/or diffuse pancreatic fibrosis. **Aim** of the study was to evaluate sIgA levels in patients suffering from CP. **Patients and Methods:** The study population consisted of 61 consecutive CP patients, observed over the period August 1995-September 1997, (51 male, 10 female; mean age 49.5±10 years). At onset of disease 63.5% of patients consumed more than 80 grams of alcohol per day (mean: 123 ± 102 g alcohol/day), while 85% of patients were smokers (mean: 24 ± 17 cigarettes/day). The mean duration of disease was 13.3 years (range: 1-37 years); 82.4% patients presented pancreatic calcifications, 43.4% diabetes, 50.9% steatorrhea and 61.4% underwent pancreatic surgery. Serum ALT and GGT were determined as well as sIgA (ELISA). Statistical analysis was carried out using the Kruskal-Wallis and Mann-Whitney U tests and the Spearman Correlation Coefficient. **Results:** sIgA were significantly more elevated in CP patients (35±23.7) than in C (11.8±4.9) ($p<0.0001$).

		Pts (N)	SigA (mg/L) (X±SD)	p	
steatorrhea	yes	28	42.1 ± 25.7	<0.0001	yes vs no and vs controls
	no	27	27.2 ± 18.6		no vs controls
diabetes	yes	23	50.8 ± 25.8	<0.0001	yes vs no and vs controls
	no	30	25.1 ± 16.9		no vs controls
surgery	yes	35	41.8 ± 25.1	<0.0001	yes vs no and vs controls
	no	22	26.6 ± 20		no vs controls
calcifications	yes	47	40 ± 24.3	<0.0001	yes vs no and vs controls
	no	10	18.3 ± 12.7		
controls	-	47	11.8 ± 4.9	-	-

sIgA were significantly more elevated in CP with steatorrhea, diabetes and calcifications and in those underwent to pancreatic surgery. sIgA did not correlate with alcohol intake or duration of disease (years) but correlated with cigarette smoking ($R=0.29$, $p=0.03$) and GGT ($R=0.46$, $p=0.0002$). 14 out of 61 (23%) CP patients had GGT values above the upper normal limit; when we analyzed only CP patients with normal GGT levels, the sIgA differences between CP subgroups remained statistically significant. **Conclusions:** This study demonstrated that sIgA is a marker of advanced chronic pancreatitis. Its value in staging CP patients needs to be further evaluated.

ENDOTHELIN RECEPTOR BLOCKADE IMPROVES MICROCIRCULATION IN ACUTE PANCREATITIS

Th. Foitzik*, H.G. Hotz, G. Eibl, J. Faulhaber, H.J. Buhr. Dept. of Surgery, Benjamin Franklin Medical Center, Freie Universität Berlin, Germany

Introduction: Microcirculatory disorders are a hallmark of severe acute pancreatitis. They are not confined to the pancreas where they promote tissue injury but can also be observed in other organs (e.g. colon, lung, liver) contributing to multiorgan dysfunction. One mediator believed to play a key role in the pathogenesis of these microcirculatory disorders is endothelin and we have previously demonstrated that endothelin receptor blockade significantly reduces mortality in acute necrotizing pancreatitis (ANP) in the rat. The aim of the present study was to further characterize the effect of a specific endothelin-1 receptor antagonist (ET-RA) on microcirculation both in and outside the pancreas.

Methods: ANP was induced in 16 rats by a standardized intraductal infusion of bile salt followed by iv cerulein over 6 hrs. Thereafter, animals were randomized for therapy with ET-RA (40mg/kg LU-135252) or NaCl 0.9% (vol. equiv.). After 24 hrs of fluid resuscitation (6ml/kg/hr Ringer's lactate) animals were relaparotomized for intravital microscopic determination of capillary blood flow (CBF) and density (CapDens), leucocyte-endothelial interaction (LR) and capillary permeability (CapPerm) in the pancreas, the mesentery and the colonic mucosa using fluorescein labelled erythrocytes and leucocytes or the plasma marker FITC dextran 150. Analysis was performed using computer-assisted techniques. Additional monitoring included cardiorespiratory and renal parameters and fluid sequestration into the third space (data not shown).

Results (mean±SEM)	CapPerm #		CBF (nl/min/cap)		CapDens (cm/cm²)		LR (cells/min)
	Colon	Pancreas	Colon	Pancreas	Colon	Mesentery	
NaCl	248±6	1.5±0.05	1.3±0.04	1.15±0.5	126±3.1	163±1.6	
ET-RA	114±5*	2.0±0.05*	1.5±0.04	1.45±0.2*	148±4.8*	7.0±1.6*	

* increase in permease; fluorescein intensity 30 min after i.v. FITC-Dextran * $p<0.05$ ET-RA vs NaCl

Conclusions: Endothelin receptor blockade significantly improves various microcirculatory parameters not only in the pancreas but also in the mesentery and colon. This is in accordance with our previous observation that endothelin receptor blockade improves outcome in the same model of ANP by counteracting systemic microcirculatory disorders, particularly capillary leakage which is believed to contribute to early organ dysfunction in experimental as well as in severe human pancreatitis. The significance of these findings is underlined by the observation that microcirculatory disorders could be observed in the presence of stable systemic cardiorespiratory parameters and up to 48 hours after pancreatitis induction in rats, suggesting that endothelin receptor blockade may even be effective when therapy is delayed.

IFOSFAMIDE CHEMOTHERAPY FOR ADVANCED PANCREATIC CARCINOMA

T. Fujiki¹*, K. Yamaguchi, K. Yamamoto, S. Akazawa, Y. Kanda, K. Futatsuki, Y. Suda²

1) Dept. of Gastroenterology, 2) Dept. of Abdominal Surgery, Saitama Cancer Center Hospital, Saitama, Japan.

Introduction: Standard chemotherapy for pancreatic carcinoma has not been established. Ifosfamide, an analogue of cyclophosphamide, has therapeutic activity against a wide variety of human malignancies. We treated the pancreatic carcinoma in a phase II trial of ifosfamide.

Patients and Methods. Patients with histologically or radiographically proven measurable locally advanced or metastatic adenocarcinoma of the pancreas were entered in the trial. Ifosfamide was administered at a dose of 1.2 to 1.5/m²/d by intravenous infusion during 60 minutes for 5 consecutive days every 3 to 4 weeks. Mesna and N-acetylcystein were not used for prevention of hemorrhagic cystitis due to receive with adequate hydration and urine alkalization.

Results. Twenty patients were entered into the study between August 1992 and January 1996. There were five men and fifteen women with a median age of 63 years (range, 43 to 77 years). Results achieved were as follows: PR in one patient, NC in 9 patients, and PD in 10 patients. The response rate was 5% and the median survival time was 17 weeks. Toxic effects included anorexia (80%), nausea and vomiting (65%), alopecia (20%), mental disturbance (20%), granulocytopenia (20%), thrombocytopenia (5%), and no renal/urological disturbance.

Conclusion. Ifosfamide was not effective for chemotherapy of advanced pancreatic carcinoma.

INDUCTION OF APOPTOSIS AND CELL CYCLE ARREST BY A NOVEL RAR ALPHA-SELECTIVE RETINOIC ACID IN PANCREATIC CARCINOMA CELLS.

K. Fujimoto*, R. Hosotani, R. Doi, M. Wada, J.-Uk. Lee, T. Koshiba, Y. Miyamoto, S. Tsuji, S. Nakajima, M. Imamura. Department of Surgery and Surgical Basic Science, Kyoto University, Kyoto, Japan.

Introduction. Recent publications have reported that all-trans retinoic acid, which almost equally binds to retinoic acid receptor (RAR) α , β and γ , inhibits pancreatic carcinoma cell growth. In this study, we used a novel RAR α -selective retinoic acid (TAC-101) as a probe to investigate the molecular mechanism of retinoid receptor function and found that TAC-101, which selectively binds to RAR α , has the growth-inhibitory effect on pancreatic carcinoma cells. To obtain informations regarding the growth-inhibitory effect of TAC-101, the induction of apoptosis and the inhibition of cell cycle progression were analyzed, and furthermore, the expression of G1-phase cell cycle-regulating factors (p21^{WAF1}, p27^{KIP1}) and the retinoblastoma gene product (pRB) and thymidylate synthase (TS), one of S-phase gene products regulated by E2F were studied.

Materials and Methods. TAC-101, molecular formula C₂₀H₂₇NO₃Si₂, was kindly gifted from Taiho Pharmaceutical CO., LTD. and used in the studies reported here. The cell growth inhibition mediated by TAC-101 in four pancreatic carcinoma cell lines (BxPC-3, MIAPaCa-2, CFPAC-1, and AsPC-1) was determined by measuring the number of cells using Coulter counter. Induction of apoptosis was confirmed by DNA gel electrophoresis and Hoechst staining. Cell cycle progression and levels of expression of p21, p27, pRB and TS proteins were analysed by flow cytometry and Western blotting, respectively.

Results. (1) Growth inhibition by TAC-101 was observed in a time- and dose-dependent manner in three cell lines, BxPC-3, MIAPaCa-2, and CFPAC-1, whereas AsPC-1 cells showed no inhibitory effect.

Table. The inhibitory effect of TAC-101 after a 6 day incubation period.

	BxPC-3	MIAPaCa-2	CFPAC-1	AsPC-1
IC ₅₀ (μ M)	13 $\pm$ 4	24 $\pm$ 6	46 $\pm$ 7	>100

(2) In TAC-101 sensitive BxPC-3 cells, DNA laddering and fragmentation were observed at 24, 48 h after TAC-101 treatment with 20 μ M. (3) In BxPC-3 cells, the population of G1 phase cells markedly increased at 48 h after treatment (control, 35.3 % and TAC-101, 81.6 %). (4) In BxPC-3 cells, a strong increase of p27 protein was detected at 24 h, and a moderate increase of p21 protein was observed at 9 h after treatment. (5) The retinoblastoma protein showed hypophosphorylated form at 24 h after treatment. (6) A decrease of TS protein was also detected at 24 h.

Conclusions. This study shows that RAR α -selective retinoic acid induces an apoptotic cell death and produces a G1 cell-cycle arrest by up-regulating p27 and p21 proteins and by preventing pRB phosphorylation, and leads to growth inhibition in pancreatic carcinoma cells.

TRANSFECTION EFFICIENCY OF NON-VIRAL VECTORS IN PANCREATIC CANCER CELL LINES

S. Fukuyama, S. Egawa, Y. Tsutsumi*, T. Mayumi*, M. Sunamura, K. Takeda, M. Kobari, and S. Matsuno

1st Department of Surgery, Tohoku University School of Medicine, Sendai, *Department of Biopharmaceutics, Faculty and Graduate School of Pharmaceutical Sciences, Osaka University, Osaka, Japan.

Introduction. The extremely poor prognosis of the patients with pancreatic cancer urges us to develop a new modality of treatments. In order to establish an in vivo transduction of therapeutic genes against pancreatic cancer, the transduction efficiencies of newly developed non-viral vectors were examined.

Materials and Methods. In vitro transfection efficiency of six kinds of cationic liposome and that of a Fusogenic liposome, which is a hybrid vector made from liposome and inactivated Sendai Virus, were examined. Purified expression plasmid that consists of LacZ gene driven by an actin promoter or a CEA promoter were used as a reporter gene. LacZ plasmids were incorporated into the fusogenic liposome and the resulting complexes were purified using glucose gradient. Two CEA positive human pancreatic cancer cell lines, PK-1 and AsPC-1, were transfected in vitro using these liposomes. After 24 hours incubation, the transfection efficiency was estimated by beta-galactosidase staining.

Results. Cationic liposomes transfected the reporter gene into the cells at various efficiency ranging from 2 to 20% which differed between the cell lines. For PK-1, the efficiency of each liposome was as follows: SuperFect[®]: about 20%, DMRIE-C[®]: about 15%, TRANSFECTAM[®]: about 9%, CellFECTIN[®]: about 8%, LIPOFECTIN[®]: about 7%, LipofectAMINE[®]: about 0.2%. While the Fusogenic liposome uniformly transfected at more than 30%. In vitro and in vivo anti-tumor effect of suicide gene therapy using these vectors will also be discussed.

Conclusion. Liposomes are considered to have some superior aspects to adopt a suicide gene therapy into clinics because of its easy maneuverability. In this study, although none of the cationic liposomes could not transfect the reporter gene into the pancreatic cancer cell lines efficiently, our data suggests that newly developed fusogenic liposome can be a new modality of treatment against pancreatic cancer

EFFECT OF OCTREOTIDE IN ACUTE PANCREATITIS - EXPERIENCE WITH SIX CASES

M. Fujimoto, H. Yamase, M. Yamaguchi, M. Yamada, M. Yoshida, S. Kurita

Gastroenterology Department, Showa Hospital, Mizunami, Japan

Introduction. Octreotide is a synthetic long-acting somatostatin analogue that inhibits exocrine pancreatic secretion. This property has led to its clinical use in the management of acute pancreatitis. Here we report on the use of octreotide in six patients with acute pancreatitis.

Patients. The cause of pancreatitis was alcoholism in 4 patients, cholelithiasis in 1 and complication of endoscopic sphincterotomy in 1. Four patients received octreotide to relieve severe abdominal pain and to prevent progression to severer pancreatitis. Two patients received octreotide to treat pseudocysts.

Management. Octreotide was injected subcutaneously in a daily dose of 400 or 200 μ g, for 3 to 10 days. All patients were also given a synthetic protease inhibitor gabexate mesilate (FOY).

Result. Four patients became free of severe symptoms 1 or 2 days after starting treatment with octreotide. In two patients with pancreatic pseudocysts, computed tomographic scans showed that the lesions had disappeared or decreased in size after octreotide administration. No case did progressed to severer disease.

Conclusion. In this study it was difficult to assess the effects of octreotide on the overall course of acute pancreatitis, because all patients concurrently received a protease inhibitor. However, octreotide markedly improved symptoms and prevented pseudocyst formation.

INVOLVEMENT OF LIPID PEROXIDATION IN SPONTANEOUS PANCREATITIS ON WBN/Kob RATS

F. Furukawa¹⁾, A. Nishikawa¹⁾, K. Kasahara¹⁾, K. Uchida²⁾, M. Takahashi¹⁾

¹⁾ Division of Pathology, National Institute of Health Sciences, Tokyo, Japan.

²⁾ Laboratory of Food and Biodynamics, Nagoya University School of Agriculture, Nagoya, Japan.

Introduction. It has been well documented that male Wistar Bonn/Kobori (WBN/Kob) rats spontaneously develop pancreatitis when they are young, and also suffer from a diabetic syndrome before 1 year of age. Lipid peroxidation has been suggested to be a possible causative factor. In order to elucidate the mechanisms of development of the pancreatic lesions, tissues from WBN/Kob rats of various ages were immunohistochemically investigated for the lipid peroxidation products 4-hydroxy-2-nonenal-modified protein (HNE-P), 4-hydroxy-2-hexenal-modified protein (HHE-P) and malondialdehyde-modified protein (MDA-P).

Materials and Methods. Male 4- to 30-week-old WBN/Kob rats were sacrificed to allow sampling of pancreatic tissues, which were fixed in cooled acetone and 10% neutral-buffered formalin and then processed for routine histopathology as well as immunohistochemistry.

Results. Although no remarkable changes were noted in younger animals, edema, hemorrhage, inflammatory cell infiltration, fibrosis, vacuolation of acinar cells and ductular proliferation were observed in the exocrine pancreas at 10, 13 and 15 weeks of age. At the ages of 20 and 30 weeks, the lesions had remarkably progressed and deposition of hemosiderin was apparent in fibrosing pancreatic tissue. Immunohistochemical examination for lipid peroxidation products showed HNE-P and MDA-P to be negative in all pancreatic tissues, but HHE-P was positive in the areas involving atrophy of acinar cells and fibrosis in the islets.

Conclusion. The results of the present study suggest that lipid peroxidation may be partially involved in the processes underlying spontaneous pancreatitis in WBN/Kob rats.

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FREQUENT ALLELIC LOSSES ON CHROMOSOME ARMS 6Q AND 12Q IN HUMAN PANCREATIC CANCER

T. Furukawa, T. Abe, M. Kimura, S. Fukushige, T. Yatsuoka, T. Yokoyama, M. Sunamura, M. Kobari, S. Matsuno, A. Horii*
Departments of Molecular Pathology and Surgery I, Tohoku University School of Medicine, Sendai, 980-8575, Japan.

Introduction Pancreatic cancer is one of the leading causes of cancer deaths in Japan as well as in western countries. Molecular mechanisms of pancreatic carcinogenesis remain largely unknown. To study pancreatic adenocarcinogenesis, allelotypes were studied in pancreatic cancers. This study led us to find frequent allelic losses in several chromosome arms including 6q and 12q.

Materials and methods Ninety-six pancreatic cancers and 20 pancreatic cancer cell lines were analyzed by means of microsatellite analysis, comparative genomic hybridization, and fluorescence *in situ* hybridization (FISH). To characterize regions that we focused on, yeast and bacterial artificial chromosomes (YAC and BAC) were employed to construct contigs to clone the deleted regions.

Results Frequent allelic losses were detected in 1p, 3p, 4q, 6q, 9p, 12q, 17p, 18q and 21q, and frequent gains were detected in 8q and 20q. Allelic losses in 9p, 17p and 18q could lead to inactivation of *p16*, *p53* and *DPC4*, respectively. However, none of the candidate genes have yet been known on 6q and 12q. Detailed analysis employing microsatellite markers spanning the entire chromosome arms 6q and 12q revealed three and two regions of common allelic loss on 6q and 12q, respectively, as follows; region A on 6q21 (<1-cM, 38/55, 69%); B on 6q23-q24 (7-cM, 33/55, 60%); C on 6q26 (13-cM, 28/55, 51%); D on 12q21 (<1-cM, 27/40, 68%), and E on 12q22-q23.1 (1-cM, 24/40, 60%). FISH analysis confirmed LOHs of these loci in pancreatic cancer cell lines and primary tumors. Regions A on 6q21 and E on 12q22-q23.1 were found to be completely covered with single YAC clone of 500-kb and 650-kb in size, respectively. These regions were also covered by BAC contigs, and mutation analyses of candidate genes in these regions are on the way.

Conclusion Putative tumor suppressor genes responsible for pancreatic carcinogenesis are very likely to exist on chromosome arms 6q and 12q.

THE EXPRESSION OF CYCLIN D1 IN PANCREATIC CARCINOMA CORRELATES WITH THE EXPRESSION OF EGF AND EGF-R.

S. Gansauge, F. Gansauge, B. Rau, and H.G. Beger
Dept. of General Surgery, University of Ulm, Germany

As we have recently shown cyclin D1 is overexpressed in human pancreatic carcinoma cells and this overexpression correlates significantly with poor prognosis ($p < 0.01$). Recent reports linked mitogenic signalling to the activation of ras which integrates growth factor signaling to the induction of cyclin D1. We assessed the role of EGF, EGF-R and cyclin D1 in pancreatic carcinoma tissues. Immunohistochemically we examined 42 adenocarcinoma tissues on the expression of EGF, EGF-R and cyclin D1 and could demonstrate an overexpression in the tumour cells in 51%, 54% and 62.3% respectively, whereas normal human pancreas stained negative for all of the three factors. Interestingly EGF as well as EGF-R expression correlated significantly with the cyclin D1 expression in human pancreatic tumour cells ($p < 0.001$ and $p < 0.05$). Cell cycle analysis in pancreatic carcinoma cell lines (BxPC 3, AsPC 1) revealed an increase of cells in S/G1-phase between 18h and 30h after stimulation with 50 ng/ml EGF. Cyclin D1 mRNA increase after 2h was shown by RT-PCR corresponding to an increase of cyclin D1 protein with the maximum level at 7.5 h following stimulation which was demonstrated by Western blot analysis. Similar results were obtained with TGF- α . By means of BrdU incorporation assays the dose dependent proliferation of the cell lines was confirmed.

Conclusion. These results demonstrate that cyclin D1 overexpression in the tumour cells of pancreatic carcinoma tissue is at least in part dependent on the mitogenic effects of EGF or TGF- α signalling through the EGF receptor. In contrast to the EGF and EGF-R expression cyclin D1 expression correlates significantly with poor prognosis suggesting that beside the stimulatory effects of EGF or TGF- α , cyclin D1 expression is influenced by other factors or by activated ras itself.

(a) PHASE II STUDY OF INTRAOPERATIVE AND CONFORMAL EXTERNAL BEAM RADIATION THERAPY IN PATIENTS WITH LOCALLY ADVANCED PANCREATIC CARCINOMA

(b) J. Furuse,¹ T. Ogino,² M. Ryu,³ T. Kinoshita,³ M. Konishi,³ S. Ishikura,² R. Sekiguchi,² and M. Yoshino¹

(c) Department of Internal Medicine,¹ Radiology,² Surgery,³ National Cancer Center Hospital East, Chiba, Japan.

Introduction. For patients with locally advanced pancreatic carcinoma, more intense irradiation with a combination of intraoperative radiation (IORT) and external-beam radiation (EBRT) has been used in an effort to improve the efficacy of radiation therapy, but the effectiveness has not been established. IORT and conformal EBRT basically deliver the radiation dose mainly to the tumor and these combination therapy is anticipated to achieve optimal dose distributions. Then the combination therapy were performed to clarify the efficacy and safety of intense radiation therapy alone.

Patients and Methods. Twenty-four patients with unresectable advanced pancreatic carcinoma localized to the pancreatic region were enrolled a phase II study of treatment with initial IORT (25 Gy) followed by conformal EBRT (40 Gy). The tumor reduction rate, as revealed by the early phase of dynamic CT, toxicity, failure pattern, and survival were evaluated.

Results. Tumor spread in the abdominal cavity was observed in 9 of 24 patients (37.5%) at laparotomy. EBRT was carried out in the other 15 patients without tumor spread. The full EBRT dose of 40 Gy was used in 12 of the 15 patients (80.0%). One patient showed a complete response, 5 partial responses (response rate: 40.0%). As to acute complications, grade 3 or worse toxicity was observed in 4 patients (26.7%). As to late complications, 1 patient had a grade 5 gastric ulcer. Hepatic metastases and local progression were observed in 9 patients each. The median survival times were 9.0 and 11.1 months, and the 2- and 4- year survival rates were 8.3% and 13.3%, 4.2% and 6.7% for all 24 patients and the 15 patients without tumor spread in the abdominal cavity, respectively.

Conclusion. The intense radiation therapy alone showed moderate anti-tumor activity with an acceptable toxicity level.

(a) ADENOVIRUS MEDIATED P53 AND P16 TRANSFER IN PANCREATIC CANCER CELLS RESULTS IN DECREASED PROLIFERATION AND INCREASED APOPTOSIS

(b) P. Ghane*¹, M. Humphreys, B. Greenhalf, N. Lemoine, JP. Neoptolemos

(c) Department of Surgery, Royal Liverpool University Hospital, 5th Floor UCD Building, Daulby Street, Liverpool, L69 3GA, UK

Introduction. Pancreatic cancer demonstrates high rates of tumour suppressor (TS) gene mutations; p53 (76%), p16 (82%) and loss of TS function. P53 and p16 both promote G1 arrest and p53 is also involved in apoptosis. The aim of this study was to replace wild-type p53 and p16 into pancreatic cancer cells.

Methods. Human pancreatic cancer cell lines; BxPc-3, Panc1, MIAPACA2 (p16-, p53-), CFPAC1 (p16+, p53-) and Capan2 (p16-, p53+) were used. The wild-type p16 expressing SW620 and wild-type p53 expressing Hep2 cell lines were also used. Therapeutic vectors were Ad5CMVp16 and Ad5CMVp53. The reporter vector, Ad5CMV β -gal, was used to assess transfection efficiency and for control infections. Therapeutic gene expression was confirmed using PCR, rt-PCR, western blotting and immunofluorescence. G1 arrest was demonstrated using flow cytometry. Apoptosis was assessed using DNA laddering and TdT labelling. Cell counts were used to plot growth curves following infection.

Results. P53 resulted in mean growth inhibition rate of 91% ± 8 (n=3+3). P16 resulted in mean growth inhibition rate of 83% ± 15 (n=3+3). The G1/S ratio was significantly higher following p16 transfer ($p < 0.001$). The apoptosis index was significantly increased for p53 ($p < 0.004$) and p16 ($p < 0.03$).

Conclusion. Adenoviral transfer of wild-type p53 and p16 results in significant growth inhibition and increased apoptosis in pancreatic cancer cells. This should represent a novel therapeutic approach.

PAIN AT THE TIME OF DIAGNOSIS AS A PROGNOSTIC SIGN FOR SURVIVAL IN PALLIATIVELY TREATED PATIENTS WITH EXOCRINE PANCREATIC CANCER

AL Grahn* & Å Andrén-Sandberg.

Department of Surgery, Lund University Hospital, Lund, Sweden

Introduction. In an attempt to identify clinically relevant and cheap prognostic factors for patients with unresectable pancreatic cancer we have investigated if a standardized measurement of pain can help.

Patients and Results. The prospective study comprises 49 consecutive patients with newly diagnosed non-resectable ductal pancreatic adenocarcinoma. There was a significant negative correlation between pain at the time of diagnosis, evaluated with a Visual Analogue Scale, VAS, and survival: the more pain the shorter survival. There was also a shorter survival for those patients with pain in the upper right part of the abdomen ($p=0.02$) or epigastrium ($p=0.02$) compared to patients without pain there, whereas pain in the upper left, lower right, and lower left parts of the abdomen as well as pain in the back or overall gave no prognostic information. The patients not using analgesics at the time of diagnosis did not live longer than those who took analgesics, and patients on morphine did not live significantly shorter than those without morphine. The type of pain (dull or colicky) and if the pain was aggravated by certain factors was of no prognostic importance. The regression analysis showed that only the size of the pancreatic tumor (tumors 2 cm or less), the type of pain (dull or colicky), and site of the pain (epigastrium) could explain some (58 %) of the correlation of VAS to survival and pain at diagnosis was an independent factor for survival when compared to stage, site, and grade of differentiation of the tumor, gender and age.

Conclusion. The measurement of intensity and extension of pain experienced at the time of diagnosis by the patient with an unresectable exocrine pancreatic cancer can be used for prognostic purposes. From this point of view the pain experienced reflects something different than the analgesics consumed.

DIAGNOSIS OF CHRONIC RELAPSING PANCREATITIS — NEW FACILITIES OF OLD METHODS.

N. Gubergits*, Y. Cherevatskaya, G. Lukashevich, Y. Zagorenko.

P. Samokhin, S. Kozhemyakin.

Department of Internal Diseases No 1, Donetsk State Medical University, Donetsk, Ukraine.

Introduction. The morbidity of chronic relapsing pancreatitis (CRP) has become considerably increased at the last 10 years. However, high probability of diagnostic mistakes remains. We decided to increase the information capacity of some existing diagnostic methods.

Patients and Methods. 220 CRP patients at the exacerbation stage and 30 non-patients were observed in our clinic. We studied their blood levels and duodenal debit part of amylase, lipase and trypsin and level of soluble fibrin-monomer complexes (SFMC) in the blood serum.

Results. 82% of the patients had normal blood levels of enzymes as their rise during the exacerbation occurred on the ground of their initially decreased concentration. With the aim to increase the sensibility of tests we were calculating indices of the enzymes deviation to the blood in relation to debit part of the enzyme in duodenum to its blood concentration. The deviation indices of CRP patients were considerably lower than in healthy people. As a result the sensibility of deviation indices reached 92% and specificity — 94%. Trypsin, entering blood stream, inhibits the formation of fibrinogen from SFMC. This results in increase of the level of SFMC in the blood serum. The level in examined patients reached 0.62 ± 0.18 Optical Units and in healthy people — 0.38 ± 0.16 Optical Units. It is important that blood level of SFMC stay high more than increase of activity of immune-reactive trypsin. Determination of SFMC in the blood needs simultaneous study of thrombocytes, as the combination of increase of SFMC index with thrombocytopenia is characteristic for consumption coagulopathy, which was diagnosed earlier with the help of SFMC determination.

Conclusion. Using of mathematical methods significantly increase the information capacity of examination of activity of pancreatic enzymes in blood and duodenum. So determination of SFMC can be used in diagnose of CRP.

PRE-DIAGNOSTIC WEIGHT LOSS IN EXOCRINE PANCREATIC CANCER. CORRELATION TO SYMPTOMS, SIGNS AND PROGNOSIS

AL Grahn* & Å Andrén-Sandberg

Department of Surgery, Lund University Hospital, Lund, Sweden

Background. Weight loss is the clinical sign most often present at the time of diagnosis for patients with pancreatic cancer

Method and results. The weight loss in 59 consecutive patients with exocrine pancreatic cancer was prospectively registered. The patients had an absolute mean weight loss of 6.8 (6.1) kg (range: 0-30 kg) correlated to the weight three months before the diagnosis and a relative weight loss of 9 (8) percent (range: 0-40 percent). There was no significant correlation between weight or Body Mass Index, BMI, and weight loss. There was a correlation of pain to weight loss when comparing patients with pain intensity of 2 or less on a Visual Analogue Scale and a weight loss of 2 kg or less. There was no difference between the weight loss for those who were possible to operate radically ($n=9$) compared to the other ($n=50$). Two of the radically operated patients were without preoperative weight loss versus nine of the others ($p=0.76$). There was no significant correlations between the patient's weight, BMI, and weight loss on one hand and origin within the gland, size, stage, and grade of differentiation of the tumor, presence of liver metastases, over-growth on the large retroperitoneal vessels or presence of diabetes or jaundice at the time of diagnosis on the other. The not radically operated patients without a preoperative weight loss ($n=8$) lived significantly longer than those with a weight loss.

Conclusion. In a prospectively collected consecutive series of patients with pancreatic cancer a smaller weight loss than earlier reported. The weight loss correlate to the pain intensity at the time of diagnosis and the absence of weight loss is a prognostically positive factor for survival.

FUNCTIONAL, NUTRITIONAL AND PSYCHOLOGICAL CHANGES IN RESPONSE TO CONVENTIONAL OR TOTAL ENTERAL NUTRITION IN PATIENTS UNDERGOING HEPATIC OR PANCREATIC RESECTIONS.

Gupta R*, Patel K, Pimrose JN, Johnson CD

University Department of Surgery, Southampton General Hospital, Southampton, United Kingdom.

Introduction: To describe changes in body composition, physiological function and psychology in patients undergoing operative treatment of hepatic or pancreatic disease consequent upon receiving total enteral nutrition (TEN) in the post-operative period.

Methods: Body fat was measured using anthropometry and Dual Energy X-Ray Absorptiometry (DEXA) scanning, respiratory function with vitalography and spirometry, muscle function with dynamometry, psychology with the Hospital Anxiety and Depression Scale (HADS), and fatigue was measured using a visual analogue scale.

Results: 30 patients were studied (15 TEN)

Table 1. Function, psychology and nutrition.

VARIABLE	Feed	Admission	Day 3	Day 7
FEV ₁ (L/sec)	Conventional	2.18±0.75	0.98±0.49	1.47±0.71
	TEN	2.29±1.03	0.82±0.58	1.44±0.72
FVC (L)	Conventional	3.0±0.8	1.3±0.7	1.9±0.8
	TEN	3.0±1.4	1.2±0.7	2.0±1.0
PEFR (L/min)	Conventional	454±109	208±95	323±121
	TEN	372±152	188±126	288±114
Grip (N)	Conventional	286±121	220±89	248±103
	TEN	289±83	225±84	248±101
Fat (DEXA-kg)	Conventional	22.1±9.9		21.6±9.6
	TEN	20.8±10.3		19.9±10.5
Anxiety	Conventional	6.9±4.2	6.2±3.7	5.9±4.8
	TEN	8.9±3.7	8.4±3.8	6.1±3.4
Depression	Conventional	4.6±3.1	6.9±3.8	6.9±4.2
	TEN	3.0±2.2	7.7±6.2	6.9±5.9
Fangue (cm)	Conventional	4.4±2.6	5.9±2.6	5.0±2.2
	TEN	4.0±2.9	7.3±1.7	6.2±1.5

All results are mean ± SD

Conclusion: Our results have demonstrated no benefit in the routine use of post-operative enteral nutrition in this patient population.

FUNCTIONAL, NUTRITIONAL AND PSYCHOLOGICAL CHANGES IN PATIENTS WITH PREDICTED SEVERE ACUTE PANCREATITIS IN RESPONSE TO TOTAL PARENTERAL OR TOTAL ENTERAL NUTRITION.

Gupta R., Patel K, Pirmrose JN, Johnson CD
University Department of Surgery, Southampton General Hospital,
Southampton, United Kingdom.

Introduction: Conventional management of predicted severe acute pancreatitis (SAP) includes intestinal rest and often requires the provision of nutritional support in the form of total parenteral nutrition (TPN). Total enteral nutrition (TEN) is known to ameliorate many of the deleterious effects of serious sepsis and may be of value in SAP. Data on the use of early TEN in SAP is presently lacking. Our aim is to assess the safety and efficacy of routine early TEN support in patients with SAP.

Methods: Patients with SAP (APACHE II score ≥ 6 on admission) were randomised to receive TPN (n=8) or TEN (n=7) within 4 hours of diagnosis by central line or naso-jejunal tube respectively. Respiratory function was measured by vitalography and spirometry (FVC, FEV₁, PEFR), muscle function by hand held dynamometry, body fat by Dual Energy X-Ray Absorptiometry (DEXA), psychological state with the Hospital Anxiety and Depression scale and fatigue was measured using a visual analogue scale.

Results: Table 1 Function, psychology and nutrition.

VARIABLE	Feed	Admission	Day 3	Day 7
FEV ₁ (L/sec)	TPN	1.45 $\pm$ 0.45	1.33 $\pm$ 0.95	1.89 $\pm$ 1.26
	TEN	1.45 $\pm$ 0.46	1.64 $\pm$ 0.54	2.38 $\pm$ 0.50
FVC (L)	TPN	1.78 $\pm$ 1.16	1.72 $\pm$ 1.21	2.44 $\pm$ 1.65
	TEN	1.79 $\pm$ 0.60	1.96 $\pm$ 0.74	2.83 $\pm$ 0.72
PEFR (L/min)	TPN	273 $\pm$ 138	234 $\pm$ 167	331 $\pm$ 218
	TEN	330 $\pm$ 154	343 $\pm$ 101	445 $\pm$ 164
Grip (N)	TPN	9 $\pm$ 4	12 $\pm$ 4	6 $\pm$ 5
	TEN	5 $\pm$ 4	5 $\pm$ 3	4 $\pm$ 4
Fat (DEXA-kg)	TPN	30 $\pm$ 13		32 $\pm$ 12
	TEN	25 $\pm$ 13		29 $\pm$ 10
Anxiety	TPN	12 $\pm$ 3	12 $\pm$ 6	10 $\pm$ 6
	TEN	9 $\pm$ 6	3 $\pm$ 3	3 $\pm$ 3
Depression	TPN	9 $\pm$ 4	12 $\pm$ 4	6 $\pm$ 5
	TEN	5 $\pm$ 4	5 $\pm$ 3	4 $\pm$ 4
Fatigue (cm)	TPN	8 $\pm$ 1	8 $\pm$ 1	4 $\pm$ 2
	TEN	8 $\pm$ 1	4 $\pm$ 1	3 $\pm$ 2

All results are mean $\pm$ SD

Conclusion: This study has shown for the first time that TEN is not only possible in patients with SAP but is as safe and efficacious as TPN.

CYTOKINE GENE EXPRESSION IN PERIPHERAL BLOOD MONONUCLEAR CELLS SUGGESTS A SYSTEMIC INFLAMMATORY RESPONSE IN ALCOHOLIC CHRONIC PANCREATITIS

Ch. Hanck, A. Hartmann, S. Rossol, M.V.Singer
Department of Medicine, University hospital of Heidelberg,
Mannheim, Germany

Introduction. The exact immune mechanisms underlying alcoholic chronic pancreatitis (ACP) remain a subject of discussion. Recent data provide evidence, that TNF- α is involved in the pathogenesis of severe alcoholic acute pancreatitis (AAP). Specific receptors regulate the biological effects of TNF- α . To define the role of cytokines we analyzed the gene expression of TNF- α and TNF- α receptors (TNFR) in isolated peripheral blood mononuclear cells (PBMC) of patients with ACP.

Patients and Methods. mRNA synthesis of TNF- α , TNFR-p55 / -p75, IFN- γ , IL-10 and inducible nitric oxide synthetase (iNOS) was determined by RT-PCR in PBMC of patients with chronic alcoholic pancreatitis. The severity of pancreatitis was evaluated according to the CT severity index (Balthazar scoring system: CTSI=1-3 n = 10; CTSI=0 n = 8); calcifications were demonstrated in 11/18 patients. 8 healthy individuals (HC) served as controls.

Results. A strong upregulation of TNF- α , TNFR-p55 and -p75 specific mRNA was found in patients with ACP compared to controls (p<0.01). 6/10 patients with AAP (CTSI 1-3) and 4/8 patients with CTSI=0 demonstrated an enhanced expression of the mRNA synthesis of IFN- γ (p=0.02). In contrast, the expression of IL-10 was not enhanced in advanced ACP; iNOS was not detectable.

Conclusion. The marked expression of TNF- α , TNFR-p55 and -p75 in PBMC suggests, that ACP provokes a systemic enhancement of inflammatory mediators.

MORPHOLOGICAL CHANGES IN THE PANCREATIC DUCTAL INNER SURFACE UNDER INCREASED PANCREATIC DUCT PRESSURE

N. Hamamoto, N. Ashizawa*, H. Endoh, Y. Kinoshita.
Dept. of Internal Medicine II, Shimane Medical University, Izumo,
Japan.

Introduction. We have demonstrated by scanning electron microscopy (SEM) that in animal models of spontaneously developing chronic pancreatitis (WBN/Kob rat, stroke prone spontaneously hypertensive rat, OLETF rat), tortuous ductal channels or helical deformities of the pancreatic ductal lumina occur, and that their inner surfaces have long cilia and crater-like depressions. These changes are thought to be caused by increased pancreatic duct pressure.

Method. The common hepatic duct of the rat was ligated proximal to its entry into the pancreas, and the common bile-pancreatic duct was also ligated near its junction with the duodenum. Using SEM, we then observed the inner surfaces of interlobular ducts in conventionally fixed pancreatic tissue 1, 2, 3, or 5 days after ligation, and corrosion casts of the pancreatic ducts 2 days after ligation.

Results. In the rats without ligation, the ductal lumina were cylindrical and their smooth inner surfaces had short cilia. At 1 day after ligation, the inner surfaces had long cilia and crater-like depressions, and at 2 days, tortuous ductal channels or helical deformities were evident. In some interlobular ducts, each epithelial cell had a bulging apical surface with a long cilium at 2 or 3 days after ligation, and at 5 days, their inner surfaces had long cilia and large crater-like depressions but no epithelial cells with bulging apical surfaces.

Conclusion. The increase of pancreatic duct pressure causes the pancreatic ductal lumen to become tortuous or helical, and the inner surface to have long cilia and crater-like depressions. Pancreatic duct cells with a bulging apical surface are present temporarily at the early stage of increasing pancreatic duct pressure.

DIAGNOSIS OF MUCIN PRODUCING PANCREATIC TUMOR BY PERORAL PANCREATOSCOPY AND INTRA-DUCTAL ULTRASONOGRAPHY

T. Hara, T. Yamaguchi, H. Ohno, Y. Hattori, T. Hirano, Y. Yosida,
S. Tsuchiya, T. Ishihara, T. Tsuyuguchi, H. Saisho.

First Department of Medicine, Chiba University, Chiba, Japan.

Introduction: Mucin producing pancreatic tumor (MPPT) is increasingly recognized in clinical entity and attention has been focused because of its unique morphology. However, there are difficulty in discrimination of the benign MPPT from the malignant, and in evaluation of its progression.

Material and Methods: Forty-seven cases were histologically confirmed as MPPT. (14 cases as invasive carcinoma, 12 cases as non-invasive carcinoma, 17 cases as adenoma, 4 cases as hyperplasia). All of them were underwent peroral pancreatoscopy (POPS) and / or intra-ductal ultrasonography (IDUS) BP30 (Olympus Co., Ltd.) and Optiscope (Clinical Supply Co., Ltd.) were used for POPS, SSD550 (Aloka Co., Ltd.) and 6Fr probe (20MHz) were used for IDUS.

Results: POPS was performed on 47 cases. Protruding lesions were detected in 29 cases (62%). According to the shapes of protruding lesions, 29 cases were classified into 5 groups (granular type, so-called "fish-eggs" type without capillary vessels, "fish-eggs" type with capillary vessels, villous type and nodular type). "Fish-eggs" type with capillary vessels, villous type and nodular type were indicated of malignancy. If the positive findings of these three types were regard as malignancy, the sensitivity, specificity, and overall accuracy were 62%, 83% and 70%, respectively. IDUS was performed on 26 cases. The protruding lesions over 2 mm in diameter were detected in 17 patients (65%). Heights of the protruding lesion were correlated with grade of malignancy. Parenchymal invasion of the tumor was evaluated by IDUS from disappearance of the pancreatic duct structure together with continuity of the tumor to the parenchyma. The sensitivity of IDUS for parenchymal invasion of the tumor was 80%, specificity was 76% and Overall accuracy was 77%.

Conclusion: Both POPS and IDUS are thought to be useful for discrimination of the benign MPPT from the malignant.

Simultaneously Resected Case of Metachronous Metastatic Pancreas and Liver Tumor from Different Origin

First Department of Surgery ¹ and Second Department of Pathology ², School of Medicine, The University of Tokushima, JAPAN
Masamitsu Harada¹, Yoh Fukuda, Seiki Tashiro, Seiji Yamasaki, Kouichi Ikawa, Tōru Kikutsuji, Keiko Yagi, Toshinobu Matsumura, Yoshiyasu Terashima and Akiko Hino²

[Introduction] Metastatic pancreatic cancer was rarely reported as difficult case of preoperative diagnosis. We had experienced a simultaneously operated case of metachronous metastatic pancreas cancer from renal cancer detected 12 years later following nephrectomy, and another metachronous metastatic liver cancer from breast cancer detected 4 years later following mastectomy. Post operative immuno histochemical study was useful to finally diagnose the metastatic lesions from different metachronous cancer origin.

[Patient and Result] A patient (72 years old female) was admitted with chief complaint of liver tumor. She received right nephrectomy for right renal cell carcinoma in 1984, and histological findings showed clear cell type. In 1989 she received left mastectomy for left breast cancer (T1N0 M0, stage I), and histological findings showed solid tubular carcinoma. Estrogen and progesterone receptor were positive. In 1993 follow up CT showed space occupying lesion in the liver (S5) suggesting metastatic tumor. Chemotherapy (CAF, UFT and Tamoxifen) was carried out and complete remission was observed. In 1995 follow up CT showed new space occupying lesion in the pancreas head, but no definite tumor was observed in the liver. The tumor of the pancreas head increased in size and tumor in the liver appeared again in 1998. Laboratory examination showed mild elevation of serum CEA (8.0 ng/ml) and severe elevation of DUPAN -II (1100 U/ml) but no elevation of CA19-9, AFP and PIVKA-II. The tumor of the pancreas head was detected as round low echic mass by US and hyper vascular mass by angiography. Main pancreatic duct showed smooth narrowing with mild dilatation of distal duct in the head of the pancreas by endoscopic retrograde pancreatography (ERP). On the other hand the liver tumor was imaged irregular shaped and low echic by US and hyper vascular by angiography. MRI showed almost same pattern of T1 and T2 image in both lesions. Patient was operated, and extirpation of the tumor of pancreas head and subsegmentectomy (S5) for liver tumor was carried out. Postoperative histological study (H.E. staining) showed pancreatic lesion as metastasis from renal cell cancer and hepatic lesion as unclear origin from renal cell cancer or breast cancer. But CEA and estrogen receptor staining showed negative response of pancreatic tumor but positive response of liver tumor to these staining. These findings proved the fact that pancreas tumor was metastasized from renal cell cancer and liver tumor was from breast cancer.

[Conclusion] Two metachronous metastatic cancer lesions in the liver and pancreas were resected simultaneously. And hepatic tumor was metastasized from breast cancer and pancreatic tumor was from renal cancer. It was very rare case. Post operative immuno histochemical and receptor staining was useful to sort out the two metastatic lesions from different origins.

DETERMINATION OF ELASTASE 1 SERUM LEVELS IN POST ERCP/EST PANCREATIC DAMAGE.

P.D. Hardt, T. Fadgyas, O. Kress, W.E. Doppl, H.P. Weber, E.A. Bimler, H. Temme*, H.U. Klör. III. Med. Department, * Department of Clinical Chemistry, Justus-Liebig-University, Gießen, Germany.

Introduction: Earlier studies using a RIA to determine pancreatic elastase 1 serum levels in acute pancreatic damage reported prolonged elevation of this enzyme as compared to lipase and amylase. The aim of this investigation was to evaluate elastase 1 as a marker of acute pancreatic damage following ERCP/EST.

Patients and Methods: Blood samples and clinical data were prospectively collected 30 min before and 40 min, 2 hrs, 6 hrs and 24 hrs after ERCP in 212 patients. EST was performed in 115 patients. Elastase 1 was analysed by ELISA (ScheboTech, Wittenberg, Germany), amylase, lipase, CRP and blood counts by standard methods. Relevant pancreatic damage was defined as CRP-elevation (> 2x normal level) in the presence of persistent abdominal pain without evidence of cholangitis.

Results: Elastase 1 time course paralleled the courses of lipase and amylase peaking at 6 hrs. There was no prolonged elevation of elastase 1. 10 of 212 patients (4.7%) had relevant pancreatic damage. Depending on the cut off used, sensitivity/specificity were as follows: lipase 80-100%/29.7-69.8%, amylase 70-90%/43.1-88.1%; elastase 1 60-90%/64.4-78.2%.

Conclusion: Elastase 1 is a marker of acute pancreatic damage similar to lipase and amylase. However, it does not provide additional information as compared to a combination of lipase and amylase.

DUODENUM-PRESERVING PANCREATIC HEAD RESECTION

- A SURGICAL TREATMENT FOR BENIGN DISEASE OF THE PANCREATIC HEAD -

N. Harada, T. Imaizumi, T. Nakasako, T. Hatori, K. Takasaki
Department of Gastroenterological Surgery, Tokyo Women's Medical College, Tokyo, Japan

Introduction. A pylorus-preserving pancreatoduodenectomy (PpPD) has been widely employed for periampullary benign disease, however, it is still too much burden for some patients with small lesion who requires pancreatic resection. This study concerns the operative procedure of our duodenum-preserving pancreatic head resection (DpPHR) and its postoperative results. **Patients & Method.** A DpPHR was carried out in 23 patients with periampullary benign disease. Twenty patients received duodenum-preserving total resection of the pancreatic head and other three patients had a resection of the inferior pancreatic head, a resection of the ventral pancreas or Beger's method. The post operative results of DpPHR were assessed in comparison with the results in a control group of 20 patients who underwent PpPD. **Results.** In the patients with DpPHR, complications developed in 5 patients (22%) and there was no mortality during hospital stay. The mean postoperative hospitalization period was 38 days, and postoperative weight gain at 6 months in comparison with preoperative one averaged 99.5%; 91% of the patients were professionally rehabilitated. These early postoperative results were acceptable compared with that of PpPD. The postoperative secretin secretion test in response to a test meal and the postoperative pancreatic function diagnostic (PFD) test in the patients with DpPHR were higher than those of the patients with PpPD. **Conclusion.** These data suggest that preservation of the duodenum contributes in part to maintain the exocrine function of the pancreas in the late postoperative course and DpPHR is feasible in some patients with benign disease who requires pancreatic head resection.

TECHNETIUM-99m-LABELED CHEMOTACTIC PEPTIDE. A NEW METHOD TO DEFINE THE SEVERITY OF ACUTE EXPERIMENTAL PANCREATITIS AND THE ASSOCIATED LUNG INJURY IN RATS

W. Hartwig, EA Carter, C Fernandez-del Castillo, J Babich, AJ Fischman, AL Warshaw

Departments of Surgery, Radiology and Pediatrics, Massachusetts General Hospital, Harvard Medical School, and Shriners Burns Institute, Boston
Leukocyte activation and infiltration are critically involved in the progression from mild to severe pancreatitis and in the development of pancreatitis-associated systemic complications such as ARDS. We investigated whether ^{99m}Tc-chemotactic peptide that binds to high affinity receptors on white blood cell membranes can determine the level of leukocyte accumulation in the pancreas and the lungs during acute experimental pancreatitis.

Methods: Pancreatitis of graded severity was induced in rats with intravenous cerulein (5 µg/kg/h, mild edematous pancreatitis) and a combination of cerulein and controlled intraductal infusion of glycodeoxycholic acid (GDOC 10 mmol/L, necrotizing pancreatitis). Saline was infused in controls. At 3 hours of infusion, ^{99m}Tc-chemotactic peptide (^{99m}Tc-For-MLFK-HYNIC) was injected intravenously. At 6 hours the pancreas and the lungs were removed and radioactivity was counted. In addition, leukocyte accumulation in both tissues was assessed by myeloperoxidase-activity and edema was determined by wet/dry ratio.

Results: The uptake of ^{99m}Tc-chemotactic peptide in the pancreas was increased in both the model of mild (p=0.04) and severe pancreatitis (p<0.001) compared to controls. Pulmonary uptake was only increased in severe pancreatitis (p=0.04). While there was only a minor increase of myeloperoxidase in the pancreas of edematous pancreatitis, a significant increase was found in necrotizing pancreatitis (p=0.003). Myeloperoxidase-activity in the lungs was increased only in severe pancreatitis (p=0.006). Pancreatic edema formation was higher in mild than in severe pancreatitis (p=0.002), and no significant differences in edema were found in the lungs.

Conclusions: Determination of ^{99m}Tc-chemotactic peptide uptake is a novel approach to differentiate acute pancreatitis of graded severity and may be preferable to labeling leukocytes with Tc^{99m} ex vivo. An increased pulmonary uptake of chemotactic peptide in severe pancreatitis indicates leukocyte accumulation in the lungs which may contribute to associated lung injury.

IN VIVO EVALUATION OF LONG TERM PATENCY OF PANCREATICOENTEROSTOMY AFTER WHIPPLE'S OPERATION

N.Hashimoto, H.Nomura, H.Ohyanaqi
Department of Second Surgery, Kinki
University, Sayama, Osaka, Japan

(Introduction) The aim of this study was to examine the long-term patency of the pancreaticoenterostomy in vivo. (Patients and method) Evaluation of the patency of the pancreaticoenterostomy was conducted in twelve patients who had undergone Whipples ope. After intravenous infusion of secretin (1.4 g/kg), the diameter of pancreatic duct was taken at 1, 3, 5, 10, 20 and 25 minute by means of ultrasonography. We estimated the degree of anastomotic stricture by the maximal dilatation ratio (MDR). [MDR: maximal value (Dmax)/ basal value (D0)]. The patients underwent PFD test before and 1-2 years after ope. (Result) pancreatic diameter after secretin: Maximal ductal dilatation was noted from 3 to 15 min after secretin infusion, thereafter ductal diameter gradually diminished and returned to its basal value at 25 min. MDR was ranged from 1.3 to 2.5, 1.7±0.12. Relationship between MDR and PFD: there was a good negative relationship between MDR and PFD. According to χ^2 analysis, we interpreted anastomotic stricture in two patient, MDR more than 2.0. In two patients peroperative value of PFD was 69.48% respectively, but postoperative value of PFD was 13.8, 18%. Except these two cases, there was no difference between pre and post operative value of PFD. (Conclusion) These data suggest that the present method allows a safe and non-invasive evaluation of the patency of pancreaticoenterostomy.

AN EXPERIMENTAL STUDY ON THE INFLUENCE OF SUPERIOR MESENTERIC GANGLIONECTOMY FOR PERIAMPULLARY CANCER ON MALABSORPTION

N.Hashimoto, H.Ohyanaqi
Department of Second Surgery, Kinki
University, Sayamashi, Osaka

(INTRODUCTION) We performed SMA (superior mesenteric artery) denervation for the purpose of radical operation for periampullary cancer. But, we have often post-operative malnutrition and diarrhea due to SMA denervation. The aim of this experimental study was to clarify the pathogenesis of malnutrition due to SMA denervation. (Material and Methods) Two group of mongrel dogs initially weighing 10-15kg were used in this study. The first group of eight dogs was denervation model. SMA was isolated distal to the common colic and inferior-pancreaticoduodenal arteries. The second group of six dogs was sham operated control group. All dogs were allowed a regular laboratory diet. At 4 weeks postoperatively, tissue level of Substance P and mucosal weight, protein, Alp, γ -GTP of small intestine were measured. (Result) In mucosal weight, protein, Alp and γ -GTP activity, the denervation group was significantly decreased compared to control. But, in the tissue level of Substance P, the denervation group was significantly higher compared to control. (Conclusion) These findings indicate that the impairment absorption following denervation was largely due to the decrease activity of membrane enzyme and increase of tissue level of Substance P.

		Mucosal weight g/10g	Mucosal protein mg/100mg	Alp activity IU/100mg	γ -GTP activity IU/100mg	Substance P ng/g muc. weight
Control	n=8	1.96±0.09	77.2±6	436.1±54	615.5	1.9±2.4
Denervation	n=8	1.41±0.04	79.6±2	614.2±19	221	12.1±4.9

Statistical significance: Denervation vs Control: *p<0.05, **p<0.01

EVALUATION OF IN VITRO CHEMOSENSITIVITY TEST IN SELECTING SUITABLE ANTICANCER DRUGS TO UNRESECTABLE PANCREATIC CARCINOMA

T.Hirano*, T.Yamaguchi, H.Ohno, Y.Hattori, T.Hara, Y.Yoshida, S.Tsuchiya, T.Ishihara, T.Tsuyuguchi, H.Saisho¹, T.Denda², H.Tokita³

¹First Department of Medicine, Chiba University School of Medicine, Chiba, Japan.

²Division of Clinical Laboratory, ³Division of Animal Research, Chiba Cancer Center, Chiba, Japan.

Introduction. The prognosis of unresectable pancreatic carcinoma is very poor. Its 1 year survival rate is estimated about 10 to 14%. To evaluate the response of anticancer drugs to tumor cells beforehand, we have developed a simple in vitro chemosensitivity test. In this study, we have investigated the clinical effectiveness of this test.

Patients and Methods. Pancreatic tissue specimens were obtained from patients with unresectable pancreatic carcinoma by percutaneous biopsy of the pancreas (PBP). PBP was carried out using the 21 gauge aspiration biopsy needle under ultrasonic guidance. The specimens were tested by rapid nuclear damage assay (RNDA). The judgment of the test was based on the morphological changes of the tumor cells nuclei after incubation in a certain concentration of anticancer drugs for 4 to 8 hours. 21 patients were enrolled in this study. 16 patients were treated with such anticancer drugs that had been determined positive chemosensitivity in the test (positive cases), and 5 patients, who had no sensitive anticancer drugs in the test (negative cases), were treated with 5-FU.

Results.

Clinical assessments of the chemosensitivity for the positive group and negative group were as follows:

	CR	PR	NC	PD
Positive (N=16)	1	2	6	7
Negative (N=5)	0	0	0	5

There was an increased tendency in duration of survival for the positive cases. **Conclusion.** This chemosensitivity test was thought to be useful for selecting anticancer drugs in chemotherapy of the patients with unresectable pancreatic carcinoma.

Contrast-enhanced endoscopic ultrasonography (CE-EUS) in the diagnosis of pancreatic diseases

Y.HIROOKA, H.GOTO, A.ITOH, S.HAYAKAWA, Y.WATANABE, Y.ISHIGURO, S.KOJIMA, S.HASHIMOTO, T.HAYAKAWA, Y.NAITOH*, 2nd Department of Internal Medicine and *Clinical Laboratory Medicine, Nagoya University School of Medicine, Nagoya, Japan.

Endoscopic ultrasonography (EUS) has made the diagnosis of the pancreatic diseases much easier, but many cases are still difficult to diagnose. As for computed tomography (CT) and magnetic resonance imaging (MRI), combined evaluation of plain and enhanced is considered important. Albunex (SHIONOGI, OSAKA, JAPAN) has been applied to clinical use as the contrast agent that can enhance US B-mode image from the intra-venous injection. Here we report the usefulness of contrast-enhanced EUS (CE-EUS) in the pancreatic disease. **{Subjects and methods}** Thirty seven patients were examined, including 11 ductal cell carcinoma, 10 mucinous cystic tumor, 4 islet cell tumor, 3 serous cystadenoma, 4 chronic pancreatitis and 5 pseudocyst. All cases were confirmed histologically either through surgery or autopsy. Lesions were examined in detail by EUS, then Albunex (0.22ml/kg) was injected to the patient intravenously. We compared the EUS image between before and after injection of Albunex and evaluated the enhanced effect of parenchyma and lesions. The apparatus used was GF-UM20 (12MHz) (OLYMPUS, TOKYO, JAPAN). **{Result}** In all cases, EUS images of parenchyma were immediately enhanced with the injection of Albunex, reached to the peak in about 3 minutes. **1) Mucinous cystic tumor;** The images of cyst-wall were more strongly enhanced than parenchyma, so the outline of the disease became clear. In all malignant cases, mural nodules in the lesion were emphasized in CE-EUS images. **2) Ductal cell carcinoma;** EUS images of lesions were not enhanced, so (true) tumor outline were cleared. In two case out of 11, pre-operative tumor staging changed to other stage by CE-EUS image. **3) Islet cell tumor;** EUS images were more strongly enhanced than parenchyma in all cases, and tumor was confirmed as islet cell tumor with the combination of plain EUS and CE-EUS image proving hypervascularity. **4) Serous cystadenoma;** All cases were enhanced in the central microcystic area in CE-EUS image. **5) Chronic pancreatitis;** All cases were enhanced as same as parenchyma. **6) Pseudo cyst;** The wall images were enhanced to the same degree as parenchyma. In one case, there was mass lesion in the cyst. CE-EUS image revealed the mass hypovascular and it proved to be pseudo-tumorous sludge. **{Conclusion}** Evaluation of plain EUS images in combination with enhanced EUS images may be useful in diagnosing pancreatic diseases

FUNCTIONAL ANALYSIS OF P53 GENE AT INITIATIVE STAGE OF PANCREATIC CARCINOGENESIS INDUCED BY APC GENE MUTATION.

M. Hirota, H. Shibata, T. Noda*

Department of Cell Biology, Cancer Institute, Tokyo, Japan.

Introduction. Although mutations of several genes, such as K-ras, p53, APC or DPC4, have been frequently identified in human pancreatic cancers, the mechanisms of carcinogenesis, which may involve loss of function of these genes, have been poorly understood. To understand a mechanism of carcinogenesis, we established a mouse model of human pancreatic cancer by conditional gene targeting in mice.

Methods. We generated a conditional mutant mouse of APC gene (APC580S) by inserting a pair of loxP sites. Recombinant adenovirus carrying Cre recombinase gene (Adex-Cre) was also constructed and used to induce a specific deletion of APC gene by injection of virus preparation directly into pancreas of APC580S. P53 mutation was also introduced by breeding APC580S with p53 deficient mice. Tumor formation was analysed by macroscopically and microscopically at certain intervals after infection.

Results. Infection of pancreas of APC580S mice by Adex-Cre induced no tumors, suggesting that loss of APC gene function may not be enough to initiate carcinogenesis. On the other hand, multiple tumor formation was observed in pancreas of APC580S mice carrying mutation of p53 gene at high frequency, when infected by Adex-Cre. These tumors were diagnosed as adenocarcinomas. Precise analysis of the process of carcinogenesis is currently under way.

Conclusion. Our results suggested that APC gene mutation may cooperate with that of p53 to induce pancreatic cancers in mice and this system may serve as a mouse model that enables us to perform precise analysis of carcinogenesis in vivo.

A TRIAL OF PROPHYLACTIC HEPATIC IRRADIATION IN PATIENTS WITH RESECTABLE PANCREATIC CANCER

S. Hishinuma, Y. Ogata, J. Matsui, I. Ozawa.

Department of Surgery, Tochigi Cancer Center, Utsunomiya, Tochigi, Japan

Introduction. We describe here our experience in a trial of prophylactic hepatic irradiation (PHI) in patients with resectable pancreatic cancer to improve survival by reducing the incidence of liver metastasis that is one of the major factors of recurrence.

Patients and Methods. Fourteen patients with pancreatic cancer have received PHI after curative resection with intraoperative radiotherapy. The entire liver was irradiated to a dose of 19.8 to 20.0 Gy with intravenous 5-fluorouracil. As a control, the 24 patients undergoing curative resection with adjuvant radiotherapy to the tumor bed were used to compare their survival.

Results. All but one patient, in whom PHI was discontinued because of severe fatigue, were able to complete the planned PHI. Two in-hospital deaths were caused by bleeding due to intraabdominal abscesses. The remaining 12 patients were discharged without major complications. Eight patients, one of whom has developed liver metastasis, are currently alive 32, 32, 31, 23, 8, 5, 4, and 2 months after surgery. Three patients, including one in whom PHI was discontinued, died of liver metastasis and peritoneal spread. One patient died of myocardial infarction without liver metastasis. Overall, 4 of the 14 patients have developed liver metastasis. However, at present, the patient group with PHI shows a significantly longer survival time than the control group.

Conclusion. It is too early to draw conclusions as to the safety and effectiveness of PHI because of the small number of patients and the short follow-up period. Nevertheless, our study suggests that PHI improves survival after curative resection.

PLASMA CYTOKINE CONCENTRATION AND ITS RELATIONSHIP TO ORGAN DYSFUNCTION IN PATIENTS WITH ACUTE PANCREATITIS

M. Hirota, F. Nozawa, A. Okabe, M. Shibata, H. Egami, M. Ogawa
Department of Surgery II, Kumamoto University Medical School,
Kumamoto, JAPAN

Introduction. Acute pancreatitis is a potentially fatal disease. The major cause of death in acute pancreatitis is multiple organ failure (MOF). It has been proposed that a prolonged and/or excessive inflammatory reaction by cytokine production may be one of the mechanisms whereby patients develop organ failure. In the present study, the concentration of cytokines and their modulators in the plasma of patients with severe acute pancreatitis and its relationship with MOF have been investigated.

Patients and Methods. Fourteen patients with severe acute pancreatitis were further subcategorized into two groups based on the number of organs with dysfunction: Group A: severe pancreatitis with dysfunction of three or more organs (n=6), and Group B: with dysfunction of less than three organs (n=8). Plasma was sampled on the days 1, 2, 3, 5, 7, 14, and 21 after admission. The concentration of cytokines and their modulators was measured by ELISA.

Results and Discussion. 1) Plasma concentration of all cytokines was higher in Group A than in Group B. Especially, that of cytokine modulators was significantly higher in Group A at admission. 2) Plasma concentration of TNF α and IL-1 β was overwhelmed by that of their modulators (sTNF-R and IL-1ra) at admission. Hence, the action of TNF α and IL-1 β might almost be suppressed (Table)

Table Plasma concentration of cytokines and their modulators

Cytokine	Group A	Group B	p (t-test)
TNF α	0.25 nM	0.02 nM	0.06
IL-1 β	0.41 nM	0.04 nM	0.04
IL-6	281 nM	4.5 nM	0.16
IL-8	147 nM	63.6 nM	0.13
IL-10	4.94 nM	1.33 nM	0.07
sTNF-R1	1.84 nM	0.33 nM	0.00001
sTNF-R2	3.64 nM	0.40 nM	0.0005
IL-1ra	565 nM	224 nM	0.002

EXAMINATION OF THE EFFECTS OF A NEW SYNTHETIC PROTEASE INHIBITOR USING A NEW DAMAGED PANCREAS MODEL IN RAT

A. Hiura¹, K. Satake²

Department of Surgery, Osaka Municipal Jusō-Shimin Hospital¹,
1st Department of Surgery, Osaka City University Medical School²,
Osaka, Japan

Introduction. We studied the trophic effects of a new synthetic pancreatic protease inhibitor (ONO-3403) on damaged pancreatic tissues by ligation of pancreatic duct of splenic lobe comparing with other pancreatic tissue without ligation in the same rat.

Method. We performed the ligation of pancreatic duct of splenic (S) lobe by 6-0 absorbable suture. Thus, gastroduodenal (GD) lobe in the same rat was left intact. These rats were divided into two groups. Group A were fed on basal diet for 4 weeks after operation; Group B on basal diet for the first three weeks and on the diet including 0.05% concentration of ONO-3403 for the next one week. Pancreatic weights in S and GD lobe were measured separately. And then the contents of protein, DNA and amylase in pancreatic tissue of each lobe were also measured 4 weeks later.

Result. In Group A, pancreatic weight and the contents of protein, DNA, and amylase in the S lobe decreased significantly compared with the GD lobe. In Group B, pancreatic weight and protein contents of each lobe increased compared with that of each lobe of Group A. Although DNA and amylase contents of the S lobe either in Group A and B showed no differences, DNA contents in the GD lobe of Group B increased compared with those of Group A.

Conclusion. These findings indicate ONO-3403 have a trophic effect on damaged and normal pancreatic tissue in the same rats. Moreover, this effect was rather hypertrophic change than hyperplasia.

NICOTINE MAY PROMOTE EXPERIMENTAL PANCREATIC CANCER IN HAMSTER

A. Hiura¹, K. Satake²

Department of Surgery, Osaka Municipal Juso-Shimin Hospital¹,
1st Department of Surgery, Osaka City University Medical School²,
Osaka, Japan.

Introduction. The epidemiologic studies have shown definite correlation between smoking and lung cancer as well as pancreatic cancer. In addition, K-ras mutation has been observed at high frequency in both cancers. However, it has not been investigated whether smoking promote the pancreatic carcinogenesis or not. We studied the effect of oral administration of nicotine on experimental pancreatic cancer in hamster.

Method. Pancreatic carcinogenesis was induced by BOP in female Syrian hamsters. The hamsters were divided into three groups. The group A were maintained on basal diet and tap water. The group B on basal diet and nicotine solution at the concentration of 0.5mVL. The group C on basal diet and nicotine solution at the concentration of 2.0mVL. All hamsters were sacrificed after 16 or 24 weeks from the first injection for histopathological studies of pancreatic lesions, i.e. carcinoma (CA), carcinoma in situ (CIS), and atypical ductal hyperplasia (ATH).

Results. The incidence of CA and CIS after 16 weeks from the first injection in the group C was significantly higher than in the group A. The incidence of CA and CIS after 24 weeks in the group C, however, was the same as in the control group. There were no significant differences in the incidence of CA between the group A and B.

Conclusion. These results indicate that nicotine has the progressive effect of pancreatic cancer in hamsters, and suggest that smoking is the one of the risk factor of pancreatic cancer.

POSSIBLE INVOLVEMENT OF MACROPHAGES IN LIVER DYSFUNCTION WITH SEVERE ACUTE PANCREATITIS

Y. Hori*, Y. Takeyama, T. Ueda, M. Shinkai, K. Takase,
M. Yamamoto, Y. Kuroda.

First Department of Surgery, Kobe University School of Medicine,
Kobe, Japan.

Introduction. Mechanism for remote organ failure in acute pancreatitis remains unclear. The aim of this study was to assess the significance of macrophages, such as peritoneal macrophages (pMΦs) and Kupffer cells (KCs) on liver dysfunction associated with acute necrotizing pancreatitis.

Methods. In male Wistar rats, KCs and pMΦs were eliminated by the intraperitoneal administration of liposome-encapsulated dichloromethylene diphosphonate (MDP). After 48 h, necrotizing pancreatitis was induced by the retrograde injection of sodium deoxycholate (DCA) into the pancreatic ducts. Then 5 h later, blood and peritoneal exudate (pancreatitis-associated ascitic fluid; PAAF) were collected. Firstly, the effects of depletion of KCs and pMΦs on liver and pancreatic functions were examined. Secondly, the cytotoxicity of the PAAF on rat primary-cultured hepatocytes were evaluated in vitro using MTT cellular proliferation assay.

Results. In the rats treated with liposome-encapsulated MDP, KCs were eliminated completely, and the number of pMΦs was reduced to 10%. Elevated levels of serum AST, ALT and LDH in the rats with DCA pancreatitis were significantly lowered by the MΦ depletion. However, serum amylase and lipase levels were not altered. Moreover, the hepatocytocidal activity of PAAF was significantly reduced by the preceded depletion of pMΦs.

Conclusion. KCs- and pMΦs-derived factor(s) possibly causes liver dysfunction in severe acute necrotizing pancreatitis.

EXPERIMENTAL STUDY OF LIVER DYSFUNCTION IN ACUTE PANCREATITIS, USING NUCLEAR MAGNETIC RESONANCE (NMR) MEASUREMENT OF CHANGES IN HEPATOCELLULAR ENERGETICS

H.S. Ho*, T. Ueda

Department of Surgery, UC Davis Medical Center, Sacramento, CA, U.S.A.

Multiple organ dysfunction (MOD) is a common cause of death associated with acute pancreatitis. Liver dysfunction in acute pancreatitis may be an intermediate step in the development of MOD or it is an end result of MOD. **Methods.** We used a ²³Na and ³¹P double-tuned NMR surface coil to continuously measure the *in-vivo* changes in hepatic intracellular Na, pH and high energy phosphates. Dysprosium-TTHA (250nM) was used to measure intracellular Na. Rats were prepared by laparotomy, with a vascular occluder around the hepatic artery and portal vein, and the surface coil on the dome of the liver. The rats were then randomized into 4 groups: control (n=4), 10-min ischemia (n=5), 20-min ischemia (n=5) and DCA-induced pancreatitis (n=5). **Results.** In rat liver, 20 minutes of total liver ischemia resulted in severe intracellular acidosis and irreversible depletion of high energy phosphates.

Effects of DCA-pancreatitis on the liver are shown in the following table (data collected at one hour after liver reperfusion or induction of pancreatitis)

	Control	10-min isch	20-min isch	DCA-pancreatitis
b-ATP/PI	0.58 ± 0.06	0.45 ± 0.05	0.11 ± 0.07*	0.20 ± 0.03*
pHi	7.48 ± 0.16	7.54 ± 0.05	6.70 ± 0.28*	6.99 ± 0.16*
Na content	22.3 ± 3	24.8 ± 4	43.9 ± 1*	59.8 ± 8.8*

* = p < 0.05 versus control, ANOVA for repeated measurements.

Conclusion. Acute pancreatitis depletes hepatocellular energetics and induces profound intracellular sodium accumulation and acidosis early in its course. The severity of such changes is similar to that induced by irreversible total liver ischemia. Liver dysfunction may be an early event of MOD in acute pancreatitis. Preservation of the liver is therefore as important as resuscitation of the cardiopulmonary system in the initial management of acute pancreatitis.

FISTULO-JEJUNOSTOMY FOR THE EXTERNAL PANCREATIC FISTULA FOLLOWING TRAUMATIC PANCREATITIS

A. Horiguchi, S. Miyakawa, K. Miura

The 2nd Dept. of Gastroenterological surgery, Fujita Health University, Toyoake, Japan.

We reported an operated case of the external pancreatic fistula following traumatic pancreatitis. A 23-year-old man was involved in traffic accident at about 12:00 midnight on December 13, 1995. He was transported to a local physician by ambulance, and was transferred to our hospital on December 15 with suspected injury of the pancreas by blunt abdominal trauma. The patient's abdomen was noted to be severe tender and muscular defence. Abdominal CT scan at admission revealed ascites and a laceration of the head of the pancreas. There was no worsening of the patient's anemia, but his vital signs remained unstable and his abdominal manifestations were severe even several hours after the admission. The patient was diagnosed injury of the head of the pancreas. Emergency laparotomy was performed to him on the same day. The peritoneal and retroperitoneal (pancreatic bed) drainage was performed. 1000 ml of bloody ascites was drained out from the abdominal cavity and retroperitoneum. Postoperative endoscopic retrograde pancreatography revealed obstruction of the main pancreatic duct of the body. Postoperative fistulography via drainage tube revealed main pancreatic duct on 28 days after operation. We succeeded in cannulation to main pancreatic duct from fistula. The second operation was performed. End to side anastomosis of pancreatic fistula to a Roux-en-Y limb of the jejunum was performed. The patient discharged on postoperative 6 months. At the present time, 28 months postoperatively, he is in good health and is living a normal daily life.

APPLEBY'S OPERATION FOR THE PANCREATIC BODY AND TAIL CARCINOMA

A. Honguchi, S. Miyakawa, K. Miura

The 2nd Dept. of gastroenterological surgery, Fujita Health University School of Medicine, Toyoake, Japan

As pancreatic body carcinoma has an invasion to common hepatic or splenic artery, the postoperation outcome of these patients has been poor because of the low resectability rate. In such a case it is sometimes difficult to complete an usual distal pancreatectomy technically and oncologically. Then we have performed radical distal pancreatectomy in 7 cases with the resection of celiac and common hepatic artery, which resembles the Appleby's technique for advanced gastric cancer.

From March 1982 to March 1996, a total of 23 patients with pancreatic body carcinoma were admitted to our department, 13 of whom underwent resection, giving a resection rate of 57%. Of the 13 patients, 7 underwent Appleby's operation. In the remaining 6 patients, distal pancreatectomy was performed. Appleby's operation with resection of the portal vein in 4, and because 1 patient had not cavernous transformation, reconstruction using the extra iliac vein. This operation with total gastrectomy was performed in 3 patients, because of direct invasion of the stomach. 1 of the 7 patients who underwent this operation, reconstruction of the common hepatic artery using inferior mesenteric vein, because of avoidance of the postoperative complications. Postoperative complications were acute cholecystitis in 1 case, AGML in 1 case that preserved stomach, acute pancreatitis in 1 case. Mortality was not found. According to the General Rules for the Study of the Japan Pancreas Society, All were more than TS3 (Tumor whose greatest dimension is more than 4.0 cm but no more than 6.0 cm). In anterior pancreatic capsule, s2 (Definite invasion) was observed in 3 patients, s3 (invasion of adjacent organs) in 3. In arterial system, a2 (invasion to the media) was observed in 4.

Conclusions: These results suggest that Appleby's operation is recommended for advanced pancreatic carcinoma in order to obtain surgically curative resection and better surgical outcome and prolonged survival with better quality of life.

EXPRESSION OF p27^{Kip1} IN HUMAN PANCREATIC CARCINOMA

Y.-X. Hu, H. Watanabe, K. Ohtsubo, Y. Yamaguchi, and N. Sawabu
Department of Internal Medicine, Cancer Research Institute,
Kanazawa University, Kanazawa, Japan.

Introduction. p27^{Kip1}, known as a tumor suppressor, has a negative regulating role of G1 progression through the cell cycle. Although abnormalities of p27^{Kip1}, including deletions and mutations, have been rarely detected, a correlation between the expression of p27^{Kip1} and the degree of malignancy has been reported in many human cancers. However, to date nothing is known of the expression of this protein and its clinicopathological significance in pancreatic carcinoma (PC). The present study is to investigate the status of the expression of p27^{Kip1} in human PC and assess the role of altered the expression of p27^{Kip1} in the development and progression of PC.

Materials and Methods. Six human normal pancreas 22 benign pancreatic lesions (18 chronic pancreatitis and 4 cystadenomas), and 54 pancreatic carcinoma (46 adenocarcinomas, 6 cystadenocarcinomas, and 2 adenosquamous carcinomas) as well as four PC cell lines were analyzed for the expression of p27^{Kip1} by immunohistochemistry (SABC) using a polyclonal antibody (C-19, Santa Cruz Biotechnology, Inc.), with a concentration of 10 µg/ml.

Results. Normal human pancreas and all except for the two cases of benign tissue showed negative-staining for p27^{Kip1} protein. Detectable expression of p27^{Kip1} was found in 13 cases (24.1%) of PC as well as 2 PC cell lines. We observed various staining of p27^{Kip1} existed among different degree of tumor differentiation, even most samples with p27^{Kip1}-negative staining having very high levels of p27^{Kip1} in well-differentiated tissues areas compared to negligible or very low levels of p27^{Kip1} in moderately or poorly differentiated areas. Moreover, the lack of the expression of p27^{Kip1} was consistently increased with increasing tumor grade (G1 & G2 vs. G3) and clinical stage (I & II vs. III & IV), respectively, and each relation had a statistically significant difference ($p < 0.05$).

Conclusion. The above results suggest that the absence of the expression of p27^{Kip1} in PC is very common and this alteration may play a role in contributing malignant progression of this disease.

SHOULD STEROID-RESPONSIVE PANCREATITIS SHOWING DIFFUSE IRREGULAR NARROWING OF THE PANCREATIC DUCT BE TERMED AUTOIMMUNE PANCREATITIS?

A. Horiuchi*, S. Kawa, K. Mukawa, Y. Ochi, N. Arakura, S. Maejima, T. Akamatsu, K. Kiyosawa
Second Department of Internal Medicine and Department of Endoscopy, Shinshu University School of Medicine, Matsumoto 390, Japan

Introduction. Although pancreatitis associated with autoimmune and related diseases has been known since Sarles and colleagues' report, autoimmune pancreatitis has not yet been defined as a clinical entity. We report 13 patients, who present an autoimmune background, with idiopathic chronic pancreatitis showing irregular narrowing of the pancreatic duct, and notify unique clinical and radiological characteristics that are remarkably distinct from those of alcoholic pancreatitis.

Patients and Methods. Over the past 5 years we have encountered 13 patients (9 men, 4 women, mean age 62.2 [range 38-75] years) who, based upon their clinical and radiological features, were diagnosed with idiopathic chronic pancreatitis showing an irregular narrowing of the pancreatic duct. We evaluated the clinical outcome of the 13 patients before and after steroid therapy.

Results. The characteristics of this type of chronic pancreatitis are summarized as follows: 1) jaundice or only mild symptoms; 2) elevated serum IgG levels; 3) swollen pancreas; 4) diffuse (or segmental) irregular narrowing of the pancreatic duct; 5) the stricture of the lower bile duct; 6) early onset of diabetes mellitus; 7) not necessarily associated with other autoimmune diseases; and 8) the functional and morphological improvements in response to steroid therapy.

Conclusion. In order to avoid unnecessary surgery, we propose that steroid-responsive pancreatitis showing diffuse irregular narrowing of the pancreatic duct should be established as a new clinical entity of chronic pancreatitis, even if it can not be termed autoimmune pancreatitis.

PANCREATIC SECRETION IN THE EARLY PERIOD AFTER PANCREATICOUDUODENECTOMY (PD)

C.J. Huang, J.S. Tang, M.J. Lin, D.C. Yeh, C.C. Wu, T.J. Liu
Department of Surgery, Taichung Veterans General Hospital, Taichung, Taiwan

Introduction. PD relieves the pancreatic duct obstruction secondary to the peripapillary tumor and partly eliminates the neurohormonal control on the exocrine function. In this study, analyzing the pancreatic secretion in the early period after PD is to study the differences in the recovery of pancreatic exocrine function in patients with narrow and dilated pancreatic duct.

Patients and Method. Four patients with narrow pancreatic duct, less than 1.5 mm in diameter, N group, and six patients with dilated duct, larger than 2 mm in diameter, D group, underwent PD were studied. The volume of pancreatic juice, electrolytes, bicarbonate, LDH, amylase and the total protein were measured in the first 6 weeks after PD. One-way ANOVA is performed for evaluating the time-related changes of these factors in the N and D groups of patients.

Conclusion. A larger volume of pancreatic juice, $p = 0.001$, and a higher daily output of amylase, p value is less than 0.05, in N group were found. Higher calcium concentration and elevated LDH in D group and a quicker recovery of bicarbonate secretion and higher protein secretion in N group were observed.

Involvement of Interleukin-6 *in vitro* Invasion of Human Pancreatic Cancer Cell

T. Idezawa, T. Kusama, H. Fujii, Y. Matsumoto.

First Department of Surgery, Yamaguchi medical university, Tamaho-cho, Nakakomagan Yamanashi, Japan.

Introduction. Although interleukin-6(IL-6) is multipotent cytokine which regulates proliferation and differentiation of certain kinds of cells, its effect on tumor invasiveness and metastasis are not clear. Using human pancreatic cancer cell line PSN-1, we investigated the effect of IL-6 on *in vitro* tumor-cell invasion.

Methods and Result. The tumor-cell invasion was assayed using Transwell chamber with 8- μ m pore-size polycarbonate membrane coated with Matrigel. The addition of IL-6 to the assay system increased the tumor-cell migration through the membrane. To characterize the migrated tumor cells, we selected two sublines derived from PSN-1 cells by chemoinvasion with IL-6, one migrated through the membrane during the first 4 h of the assay(H cell) and the other remained in upper chamber until 24 h(L cell). We performed the same selection five times and isolated two clones(5H and 5L). The invasion of 5H cells was an approximately three times as high as that of 5L cells. In morphological observation of 5H cells, typical cells were fusiform shape and extended processes. The addition of conditioned medium(CM) prepared from 5H cells potentiated the invasion of 5H and 5L cells, however, the effect of CM from 5L was lesser effective. CM prepared from 5H also caused a morphological change in parent PSN-1 and 5L cells to 5H cell like formation. The growth rate of these tumor cells was not affected by the incubation with CM from 5H cells. The level of IL-6 in CM prepared from 5H cells measured by ELISA method was 27.7ng/ml, which was an approximately 16 times as high as that from 5L cells(1.69ng/ml).

Conclusion. 5H cell produced in its conditioned medium high level of IL-6 which induced morphological change and enhanced *in vitro* invasion of PSN-1 cells.

EXPERIMENTAL STUDY ON THE MECHANISM OF PROGRESSION OF ACUTE PANCREATITIS FROM THE STANDPOINT OF CHANGES IN EICOSANOIDS, AND EFFICACY OF ADMINISTRATION OF OKY-046, OP-2507, AND ONO-4057

T. Iida, T. Higashiguchi, S. Isaji, H. Yokoi, Y. Kawarada
First Department of Surgery, Mie University School of Medicine

Introduction Involvement of eicosanoids, which are product of arachidonic acid metabolism, has been pointed to as one of the mechanisms of progression of acute pancreatitis(AP). We therefore created experimental pancreatitis in rats, focused our attention on changes in thromboxane A₂(TxA₂), prostaglandin I₂(PGI₂), and leukotriene B₄(LTB₄), administered a TxA₂ synthesis inhibitor(OKY-046), PGI₂ analog(OP-2507), and LTB₄ receptor antagonist(ONO-4057), and investigated the mechanism of progression of AP and their inhibitory effect.

Methods 1) **Experimental group:** Male Wistar rats were used. Group A: AP induced by injecting of trypsin-taurocholate mixed solution into the pancreatic duct; Group B: OKY-046(100mg/kg) injected subcutaneously(SC) every 12 h beginning immediately after the inducing AP; Group C: OP-2507(100 μ g/kg) injected SC every 12 h beginning immediately after the inducing AP; Group D: ONO-4057(100mg/kg) given orally 30 min before the inducing AP. 2) **Parameters investigated:** Survival rate (all groups:n=12), and be serial sacrifice and necropsy (all groups:n=8), determination of plasma phospholipase A₂ (PLA₂) activity, determination of TxB₂, 6-keto prostaglandin F_{1 α} (6-KF) and LTB₄ in plasma, pancreas, lungs and kidney tissue, and investigation of histological changes in the pancreas, lungs and kidneys.

Results 1) **Survival rate:** The rates 24 h later were: Group A 33.3%; Group B 83.3%; Group C 58.3%; Group D 66.7% and the survival rate in Group B was significantly better than in Group A. 2) **Plasma PLA₂ activity:** Activity increased in every group after induction of AP, but was significantly lower in Groups B and D than in Group A. 3) **TxB₂, 6-KF, LTB₄:** ① Changes in plasma: All levels increased in every group, but after 12h TxB₂ was significantly lower in Group B than in Groups A, C and D, and LTB₄ was significantly lower in Group D than in Groups A, B and C. ② Changes in tissue: After 12h, TxB₂ (pg/mg protein) in pancreas and lung tissue was 66.5 and 948.4 in Group B, significantly lower than in Group A (141.1; 1780.1), but the values in Groups C and D were almost as high as in Group A. LTB₄ was similarly high in Groups A, B and C, but significantly lower in Group D(42.3; 92.6) than in Group A(87.0; 169.0). 6-KF values in pancreas and lung tissue were high in all groups, and the changes in TxB₂, 6-KF and LTB₄ in kidney tissue were slight in all groups. 4) **Histological changes:** Pancreatic hemorrhagic necrosis and pulmonary alveolar degeneration were most severe in Group A, and mildest in Group B. **Conclusion** An adequate suppressive effect was not obtained by administration of PGI₂, which possesses a cytoprotective action, or the LTB₄ receptor antagonist alone. However, TxA₂ plays the largest role in the progression of lung injury, and administration of OKY-046 reduced TxA₂ production and improved the survival rate in severe pancreatitis.

K-RAS MUTATIONS IN THE DUODENAL JUICE : IS IT A USEFUL DIAGNOSTIC TOOL FOR PERIAMPULLARY CANCERS?

H. Iguchi, K. Sugano*, T. Akashi, A. Funakoshi, H. Wakasugi.

Division of Gastroenterology, National Kyushu Cancer Center, Fukuoka, *Division of Clinical Laboratory, National Cancer Center Hospital, Tokyo, Japan.

Introduction. Prognosis of pancreatic cancer is one of the poorest among various cancers. This is, in part, due to lack of a diagnostic tool to detect pancreatic cancer earlier although radiological imaging has made marked progress. We analyzed K-ras mutations in the duodenal juice(DJ) in order to evaluate its usefulness as a diagnostic tool for periampullary cancers.

Patients & Methods. One hundred and fifty-one patients admitted to the National Kyushu Cancer Center were studied. These include 33 pancreatic cancer, 3 biliary cancer, 2 ampullary cancer, 7 pancreatic cyst, 77 chronic pancreatitis and 27 other benign disorders. DJ was collected under a 60-min intravenous infusion of 100U secretin. DNA was extracted from the pellet after centrifugation of DJ, and mutations of the K-ras codon12 were analyzed using enriched PCR by Bst-N1 digestion (Gastroenterology 110: 221, 1996).

Results. In the patients with periampullary cancers, mutations were detected in 22(63%) of 35 pancreatic cancer, 2(67%) of 3 biliary cancer and 1(50%) of 2 ampullary cancer. Whereas such mutations were detected only in 8(7.4%) of 111 benign disorders(1(14%) of 7 pancreatic cyst, 5(6.5%) of 77 chronic pancreatitis and 2(7.4%) of 27 other benign disorders).

Conclusions. K-ras mutations are identified in non-cancerous lesions of the pancreas, and in the analysis using pancreatic juice(PJ), in fact, mutations are detected even in benign pancreatic disorders with relatively high frequency. In the present study, a positive rate for the K-ras mutations is 63% in the periampullary cancers, while it is less than 10% in the benign disorders. Further, collection of DJ is less invasive to patients than that of PJ. These results suggest utility of analysis of the K-ras mutations in DJ to differentiate periampullary cancers from benign conditions.

A SPECIFIC INHIBITOR OF NEUTROPHIL ELASTASE (ONO-5046) CAN HARDLY IMPROVE ORGAN DAMAGE IN ACUTE HEMORRHAGIC PANCREATITIS IN DOGS

M. Imamura*, Y. Mikami, H. Takahashi, H. Yamauchi.

Department of Surgery, National Sendai Hospital, Sendai, Japan.

Introduction. It is known that neutrophil (PMN) elastase induces tissue damage of remote organs in acute severe pancreatitis. Therefore, in this study the therapeutic effect of ONO-5046 on the lung, liver and kidney in addition to the pancreas was examined in severe hemorrhagic pancreatitis in dogs. **Materials and Methods.** Eleven adult beagle dogs were used for the study. Under general anesthesia, acute hemorrhagic pancreatitis was induced by injection of a mixture of autologous bile and porcine trypsin into the main pancreatic duct. Additionally, lipopolysaccharide(LPS:2mg/kg) was administered intravenously at 2 hrs after induction of pancreatitis. For one group, continuous i.v. infusion of ONO-5046 (50mg/kg/hr) was started prior to the injection of LPS (ONOgroup). For the other group (control), saline was infused instead. Over a 6-hr period, blood samples were taken from the femoral artery and the blood pressure was monitored. Finally, the pancreas, lungs, kidneys and a lobe of the liver were removed, weighed and used for histological examinations. **Results.** There was a large amount of bloody ascites. WBC count was markedly reduced in response to induction of pancreatitis, and decreased further by the septic attack in the two groups. Serum levels of amylase and α 2-macroglobulin-trypsin complex increased similarly in both groups. Wet weight of the lung was slightly heavier in the controls. Microscopically, the pancreas showed interstitial hemorrhage accompanied by extensive edema in both groups. Mild inflammatory cell infiltration and bile stasis occurred in the liver of the controls. The lung demonstrated mild inflammatory cell infiltration in the two groups. **Conclusion.** It is presumed that severe hemorrhagic pancreatitis can not be alleviated by administration of an inhibitor of neutrophil elastase alone, though it tended to lessen the damage of remote organs such as the liver and lung.

ROLE OF INTRADUCTAL ULTRASONOGRAPHY IN DIAGNOSIS OF CYSTIC LESIONS OF THE PANCREAS

K. Inui*, S. Nakazawa, J. Yoshino, K. Okushima, Y. Nakamura, T. Takashima, T. Hattori¹ and H. Misoyoshi¹

Dept. of Internal Medicine, Fujita Health University, Nagoya, Japan.

¹ Dept. of Gastroenterology, Yamashita Hospital, Ichinomiya, Japan

Introduction. Intraductal ultrasonography (IDUS) is expected as a precise diagnostic method for diagnosis of pancreatic diseases. We evaluate the usefulness of differential diagnosis for pancreatic tumors, including mucin producing tumors.

Patients and Methods. We performed IDUS on 71 patients revealed pancreatic cyst, dilatation or stenosis of the main pancreatic duct with extracorporeal ultrasonography (US) or endoscopic ultrasonography (EUS) from 1993 to 1997. We inserted miniature probes into the main pancreatic duct (MPD) through a biopsy channel of a duodenoscope after endoscopic retrograde pancreatography (ERCP). We used the ultrasonic probe UM-3R (20 MHz, 2.4 mm in diameter) and UM-4R (20 MHz, 2.0 mm), developed by Olympus. We studied the usefulness of IDUS in differential diagnosis of the pancreas disease.

Results. 71 patients were diagnosed clinically with ERCP, EUS, follow-up study or surgery; 4 patients had pancreatic cancer (common type), 7 pancreatolithiasis, 12 chronic pancreatitis, 4 duodenal papilla carcinoma, 36 pancreatic cysts, and 2 miscellaneous. Six patients were diagnosed as normal lesions with IDUS. Ten of 36 patients with cysts underwent surgical resection, 4 patients were adenocarcinoma, 2 adenoma and 2 hyperplasia. IDUS revealed mural nodule, mucus echos, and solid tumor with mixed pattern in patients with intraductal adenocarcinoma. These findings were helpful to distinct mucin producing pancreatic cancer from adenoma or hyperplasia.

Conclusion. IDUS is very useful for differential diagnosis of pancreatic cysts, and for diagnosis of cancer extension of intraductal papillary tumor of the pancreas. IDUS is recommended as the third examination for cystic lesions of the pancreas after EUS or ERCP.

NICOTINAMIDE IS MORE EFFECTIVE UNDER HYPERGLYCEMIC STATE FOR THE PROTECTION OF SYNGENEICALLY TRANSPLANTED ISLETS

M. Ishigame, Y. Ogawa, Y. Umada, Y. Tazawa, Y. Katayama*, T. Nakamura, T. Suda. Hirosaki Univ. School of Medicine, Hirosaki, *Hachinohe City Hospital, Hachinohe, Japan

Introduction. Administration of Nicotinamide (NA) prevents NOD mouse from overt diabetes and the trial of NA in recent-onset IDDM has started. As to islet transplantation (Tx), the survival rate of islet graft is not satisfied. So we examined whether NA is protectable for the survival of syngeneic islet grafts.

Method. Non diabetic and 65mg/kg streptozotocin-induced diabetic rats were transplanted 1000 syngeneic islets under the renal capsule. They were treated with 0.5g/kg NA or saline intraperitoneally for 7 days. The blood glucose (BG) levels at 0, 3, 7, 14 days after Tx were compared in these 4 groups. Oral glucose tolerance test (OGTT) was performed at day 14. Grafts were removed at day 3 for the detection of DNA fragmentation, and at day 15 for the measurement of insulin contents and morphological examinations.

Results. Non-fasting BG levels of diabetic with NA group is significantly lower than those of diabetic without NA group at day 7 and 14 (78±4mg/dl vs 246±54.1mg/dl at day 14). BG levels of diabetic with NA group after glucose loading were also lower than those of diabetic without NA group. Insulin contents of diabetic with NA, diabetic without NA, non diabetic with NA, non diabetic without NA, freshly isolated 1000 islets were 29±7, 7±2, 6±1, 5±1, 22±3 µg, respectively. Morphologically, vacuolated degeneration and apoptotic change were observed in the grafts of diabetic without NA group.

Conclusion. NA has the beneficial effects on the islet graft especially in diabetic state, and might be a useful tool for islet Tx.

BACTERIAL INFECTION AND EXTENT OF NECROSIS IN SEVERE ACUTE PANCREATITIS DETERMINANTS FOR ORGAN FAILURE

R. Isemann, B. Rau, H.G. Beger

Department of General Surgery, University of Ulm, Germany

Besides the presence of necrosis, organ failure (OF)/multi organ failure (MOF) is an important factor for the severity determination of acute pancreatitis. As the relationship between OF/MOF and both the extent of necrosis and the incidence of infection of pancreatic necrosis has not been well defined, we aimed to address this issue in the present study.

Patients and methods: 300 pats with contrast-enhanced CT (CECT) and/or intraoperatively proven NP treated at our hospital during 03/82 to 12/96 were analyzed for the occurrence of the following complications: pulmonary, renal, and cardiocirculatory insufficiency, sepsis/sepsis-like syndrome (SLS), and coagulopathy. The extent of intrapancreatic necrosis demonstrated by CECT was graded into < 30% (group A), 30%-50% (group B), and > 50% (group C). Infection of pancreatic necrosis was identified by either fine-needle aspiration and/or intraoperative smears.

Results: Out of 300 pats clinical and radiological data were obtained from 225 pats (151m, 74f, mean age 51.4 years) with necrotizing pancreatitis, who had a mean admission Ranson-score of 4 (range 0-10). Infection of necrosis was found in 73 (32%) pats. Mortality was 23.4% in the infected and 13.0% in the sterile group. The overall incidence of OF was significantly higher in pats with infected compared to those with sterile necrosis (90% vs 73%, p=0.003) as were the following organ/systemic complications: pulmonary insufficiency (73% vs 58%, p=0.02), sepsis/SLS (57% vs 38%, p=0.006), and coagulopathy (54% vs 36%, p=0.008), respectively. With respect to the extent of intrapancreatic necrosis demonstrated by CECT, OF occurred more frequently in pats of group C compared to group A or B (97% vs 31% and 21%, p=0.003). In instances of sterile necrosis a correlation was found between the incidence of OF and the extent of intrapancreatic necrosis (group A: 36%, group B: 74%, group C: 96%, p<0.05), whereas this was not observed in pats with infected necrosis (group A: 88%, group B: 86%, group C: 96%).

Conclusion: OF is a frequent finding in severe acute pancreatitis. The incidence of OF correlates with both extent and infection of necrosis. Pats with infected necrosis carry a significantly higher risk to develop OF, whereas in pats with sterile necrosis the incidence of OF is related to the extent of necrosis.

ESTIMATION OF SECRETORY BICARBONATE FLUX FROM GUINEA-PIG PANCREATIC DUCT CELLS

H. Ishiguro*, S. Naruse, M. Kitagawa, Y. Nakae, H. Ieda, O. Ito, Y. Seki, S.B.H. Ko, N. Mizuno, T. Yoshikawa, M. Mori, M. Nakashima, T. Hayakawa, M.C. Steward*

Internal Medicine II, Nagoya University School of Medicine, Nagoya,

Japan and *School of Biological Sciences, University of Manchester, Manchester, UK

Introduction. Secretin evokes HCO₃⁻-rich fluid secretion from intra- and interlobular pancreatic ducts. To quantify the secretory flux of HCO₃⁻ from the duct cells, we have monitored luminal pH (pH_L) and luminal volume (V_L) simultaneously in isolated interlobular duct segments.

Methods. Isolated ducts were prepared from guinea-pig pancreas and their ends sealed spontaneously during overnight culture. The lumen was punctured with a double-barreled pipette, and the luminal fluid was replaced with a solution containing the pH-sensitive dye BCECF-dextran. pH_L was measured by microfluorometry and V_L by particle analysis of fluorescent images. Calibration of V_L was performed using a nanoliter-syringe driver (Sutter Instruments). The rate of fluid secretion was estimated from the changes in V_L and was expressed as secretory rate per unit area of epithelium. The flux of HCO₃⁻ to the lumen was calculated from the rate of change of pH_L, the luminal buffering capacity and the secretory rate.

Results. When ducts were superfused with a HCO₃⁻-buffered standard solution (pH 7.4, 25 mM HCO₃⁻/75 % CO₂) and the lumen was filled with a solution containing 125 mM HCO₃⁻ and 23 mM Cl⁻ (pH 8.2, 5 % CO₂), spontaneous fluid secretion was 1.03 ± 0.20 nl/min/mm² (mean ± S.E.M., n = 4) and pH_L decreased slowly from 8.12 ± 0.05 to 8.04 ± 0.03 in 5 min. The calculated HCO₃⁻ flux in the final minute was 0.02 ± 0.01 nmol/min/mm² and the estimated concentration of HCO₃⁻ in the secreted fluid was 24 ± 9 mM. When 10 nM secretin was applied, the secretory rate increased to 1.89 ± 0.33 nl/min/mm² and pH_L increased to 8.21 ± 0.04 in 8 min. The calculated HCO₃⁻ flux at the end of this period was 0.32 ± 0.07 nmol/min/mm² and the estimated concentration of HCO₃⁻ in the secreted fluid was 149 ± 13 mM.

Conclusions. When the duct lumen was filled initially with a HCO₃⁻-rich solution, a Cl⁻-rich fluid was secreted spontaneously. On stimulation with secretin, the secretory rate increased and the composition of the secreted fluid changed from Cl⁻-rich to HCO₃⁻-rich. The ability to quantify HCO₃⁻ secretion in isolated interlobular ducts will be useful in studying the mechanism of HCO₃⁻ secretion in pancreatic duct cells.

IMMUNOLocalIZATIONS OF TRANSFORMING GROWTH FACTOR β 1, MATRIX METALLOPROTEINASES, TISSUE INHIBITORS OF METALLOPROTEINASES AT PANCREATIC DUCTS IN CHRONIC PANCREATITIS

T. Ishihara*, A. Hayasaka, T. Yamaguchi and H. Saisho
First Department of Medicine, Chiba University School of Medicine, Chiba, Japan

Introduction. The progression of fibrosis in chronic pancreatitis is still obscure. To reach a better understanding of this problem, we investigated the immunolocalizations of type IV collagen (Col-IV) and laminin around pancreatic ducts, and those of matrix metalloproteinase-2,9 (MMP-2,9), tissue inhibitors of metalloproteinase-1,2 (TIMP-1,2), and transforming growth factor β 1 (TGF β 1) at the ductal epithelia in chronic pancreatitis.

Methods. This study included 20 surgical specimens of fibrotic pancreas from patients with chronic pancreatitis and 5 normal samples from autopsy cases. Immunostaining was performed by the streptavidin-biotin method after antigen retrieval. We evaluated the staining patterns and the percentage of positive cells of each antigen.

Results. In chronic pancreatitis, the immunostainings of Col-IV and laminin along the basement membrane (BM) of pancreatic ducts were disrupted in 11/20 (55%) and 8/20 (40%) respectively, whereas no disruption was detected in normal pancreas. Positive immunostainings for MMP-2, MMP-9, TIMP-1 and TIMP-2 in ductal epithelia were 15/20 (75%), 5/20 (25%), 4/20 (20%) and 10/20 (50%) respectively, whereas no immunostaining was seen in normal pancreas. The staining intensity of MMP-2 in ductal epithelia was associated with the staining intensity of Col-IV around the pancreatic ducts. Also, the staining intensity of MMP-2 was progressively increased in proportion to the staining intensity of TGF β 1.

Conclusion. These findings suggest that TGF β 1 induced in pancreatic duct cells also induced MMP-2 in an autocrine or paracrine manner, and that this MMP-2 decomposed Col-IV of the BM of pancreatic ducts in chronic pancreatitis. The disruption of Col-IV of the BM may relate to the injury of pancreatic ducts, and finally cause the progression of the inflammation and the fibrosis.

ANTI-ANGIOGENIC THERAPY FOR THE TREATMENT OF BLOOD-BORNE AND DISSEMINATED METASTASES OF PANCREAS CANCER: AN *IN VIVO* MODEL

H. Ishikura*, Y. Kawarada, H. Kato, T. Yoshiki, H. Kato
Departments of Pathology and Surgery, Hokkaido University School of Medicine, Sapporo, Japan

Introduction. Recent investigations have revealed a critical importance of tumor-induced angiogenesis in establishing grossly visible, clinically harmful metastatic nodules. The intervention of angiogenesis may thus improve quality of life of patients with pancreas cancer.

Methods. An anti-angiogenic agent, TNP-470, 30 mg/kg, or vehicle solution only was administered to immunodeficient mice. Animals had been inoculated 1×10^4 of pancreatic carcinoma cell line, PCI-43 into the spleen. Animals were killed 6 or 10 weeks later, and numbers of metastatic nodules per liver volume were calculated by the formula by Enzmann et al. The proliferation and apoptosis of tumor cells were estimated by PCNA staining and TUNEL method. In another experiment, a dissemination-prone PCI-43 subline (PCI-43p3) was established by a repetitive selection of peritoneal implants. TNP-470, 30 mg/kg, or vehicle solution was administered in animals that had been inoculated 1×10^7 PCI-43p3 *i.p.*, and disseminated nodules in the peritoneum were grossly and histologically examined 4 weeks later.

Results. Numbers of metastatic liver nodules were suppressed in the TNP-treated groups of 6 (370 $\pm$ 284 vs 23 $\pm$ 9) and 10 (197 $\pm$ 99 vs 36 $\pm$ 27) weeks-observation, when compared with control mice. Suppression of proliferation and increase of apoptosis was found in the TNP-treated groups. Peritoneal dissemination was also suppressed in the TNP-treated animals (11.1 $\pm$ 2.6 vs 1.3 $\pm$ 1.0). TNP-inoculated animals exhibited a weight loss.

Conclusion. Anti-angiogenic treatment exhibited a suppressive effect on blood-borne and disseminated metastases of pancreas cancer in animal models.

INTRAOPERATIVE CYTODIAGNOSIS FOR DETECTING A MINUTE INVASION OF THE PORTAL VEIN DURING PANCREATODUODENECTOMY FOR ADENOCARCINOMA OF THE PANCREATIC HEAD:

O. Ishikawa, H. Ohgashi, H. Nakano, Y. Sasaki, H. Furukawa, S. Imaoka. Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan

Introduction. During the pancreaticoduodenectomy for adenocarcinoma of the pancreatic head, we frequently encountered cases in which the superior mesenteric-portal venous confluence (SMPVC) was involved with cancer. With regards to the indication of the concomitant SMPVC-resection, as suggested by recent papers, a better long-term outcome would be expected if the cancer invasions are limited to the tunica adventitia or media of the SMPVC wall. This raised fears whether or not such a small SMPVC-invasion might have always been detectable by a macroscopic inspection alone.

Patients and Results. We have performed an intraoperative cytology on the touch smear of the exposed SMPVC wall for 23 patients with pancreatic head cancer. All of their SMPVCs were separated from the pancreatic head and appeared to be intact at a macroscopic level. As a result of this examination, 7 patients (30%) were newly judged as having cancer cells on the SMPVC wall and they received an additional resection of the SMPVC. Postoperative histology indicated that cancer invasion into the SMPVC wall was present in 6 out of 7 patients, and that their cancer invasions were limited in the tunica adventitia (5 patients) or tunica media (one patient) of the SMPVC wall. **Conclusion.** In order not to miss the chance of a cure by SMPVC-resection, our intraoperative cytology for the touch smear of the SMPVC is worth performing more actively for the intact-looking SMPVC during the resection of pancreatic cancer.

OVEREXPRESSION OF BONE MORPHOGENETIC PROTEIN-2 IN HUMAN PANCREATIC CANCER CORRELATES WITH DECREASED PATIENT SURVIVAL.

T. Ishiwata¹, J. Kleeff², H. Friess², M.W. Büchler², and M. Korc¹.

¹Division of Endocrinology, Diabetes and Metabolism, Departments of Medicine, Biological Chemistry and Pharmacology, University of California, Irvine, California 92697, USA; ²Department of Visceral and Transplantation Surgery, University of Bern, Switzerland.

The transforming growth factor-beta (TGF- β) family consists of a large group of polypeptides that includes 3 mammalian TGF- β isoforms, activins, inhibins and bone morphogenetic proteins (BMPs). These polypeptides play an important regulatory role in tissue growth and development. TGF- β s are known to be overexpressed in human pancreatic cancer and this overexpression has been correlated with enhanced tumor aggressiveness. It is not known, however, whether other members of this superfamily also contributes to disease progression in this disorder. Therefore, in the present study, we characterized the expression of BMP-2 in pancreatic cancer cell lines and tissue samples, and correlated the presence of BMP-2 in the cancer cells with patient survival. Northern blot analysis revealed the presence of a single 3kb BMP-2 transcript in all five tested pancreatic cancer cell lines. Furthermore, BMP-2 enhanced the growth of two cell lines (CAPAN-1 and ASPC-1), inhibited the growth of one cell line (COLO-357) and was without effect in the other two cell lines (PANC-1, T3M4). Densitometric analysis of Northern blots using RNA samples from 24 cancers and 18 normal pancreatic tissue samples revealed a 10-fold increase ($p < 0.001$) in the 3 kb BMP-2 transcript in the pancreatic cancers in comparison to normal controls. The mean survival of patients whose pancreatic cancers expressed BMP-2 in the cancer cells was 10 months. In contrast, the mean survival of patients whose pancreatic cancer cells were negative for BMP-2 immunoreactivity was 16 months. These findings indicate that BMP-2 is overexpressed in human pancreatic cancer, that BMP-2 has the capacity to modulate pancreatic cancer cell growth, and that BMP2 might contribute to disease aggressiveness in human pancreatic cancer.

CALCIUM-EVOKED GASTRIN RELEASE FROM GASTRINOMA CELLS IS MEDIATED VIA CALCIUM-SENSING RECEPTOR

A. Itami, M. Kato, R. Doi, R. Hosotani, M. Kogire, Y. Shimada, M. Imamura.

Department of Surgery and Surgical Basic Science, Kyoto university, Kyoto, Japan

Introduction. We have been studying the fundamental rationale for the useful SACI test (selective arterial calcium injection test) for the preoperative localization of endocrine tumors of the pancreas. Recently, we have clarified that human insulinoma cells possess calcium-sensing receptors (CaR) which might play an important role in the clinical SACI test as well as in *in vitro* responses (Kato, *et al Surgery*, 1997). In the present study, we testified whether CaR plays a similar role in human gastrinoma cells.

Methods. Human gastrinoma cells were taken from mechanically minced gastrinoma tissues which were obtained at surgery. Following studies were performed. 1) Gastrin secretory dynamics in response to the increase in the concentration of extracellular calcium ($[Ca^{2+}]_o$) from 2.54 to 10 mM were observed in the perfusion system. 2) The change of the concentration of cytosolic free calcium ($[Ca^{2+}]_i$) was monitored by fluorometry using fura-2, when the $[Ca^{2+}]_o$ was changed from zero, 2.54, 5 to 10 mM. 3) Total RNA was extracted from frozen human gastrinoma tissues, and was subjected to RT-PCR with CaR-specific primers followed by Southern blot hybridization.

Results. 1) High $[Ca^{2+}]_o$ evoked a drastic increase in gastrin release from gastrinoma cells and the peak secretory rate was 2-fold of the basal level. 2) As the $[Ca^{2+}]_o$ increased, the $[Ca^{2+}]_i$ in gastrinoma cells rapidly elevated in a dose-dependent manner. 3) RT-PCR analysis demonstrated the appropriate 682 bp CaR products.

Conclusion. Our data suggest that CaR might be involved in the mechanism for the $[Ca^{2+}]_o$ -evoked gastrin release and the increase in $[Ca^{2+}]_i$ in human gastrinoma cells.

FLUORESCENCE IMAGES OF PANCREATIC DUCTS BY AUTOFLUORESCENCE ENDOSCOPIC IMAGING SYSTEM

K. Izuishi¹, M. Ryu¹, H. Tajiri², T. Abe², T. Kinoshita¹, M. Konishi¹, H. Inoue¹, J. Furuse², Y. Maru². Department of Surgery¹ and Internal Medicine², National Cancer Center Hospital East, Chiba, Japan

Introduction. Gastrointestinal neoplastic tissue has been reported to exhibit intrinsic autofluorescence that differs from the autofluorescence of normal tissue when excited with blue or violet light. A endoscopic autofluorescence imaging system (LIFE-GI system; Xillix technology Corp., Canada and Olympus optical Co., Japan) that uses mercury light for excitation has been newly developed for imaging lesions of dysplasia and carcinoma in the gastrointestinal tract. However, in pancreatic duct, it has not been applied to pancreatic duct. This is the first report on autofluorescence endoscopic imaging system in the pancreatic duct.

Patients and Method. Two cases of pancreas cancer and chronic pancreatitis are presented. After pancreatectomy, we put endoscope (12 Fr.) in the pancreatic duct of resected pancreas. Then, the images were obtained by the LIFE-GI system (excitation, 437 nm).

Results. In a patient of pancreas cancer, the image of cancer lesion in pancreatic duct was seen in dark red in comparison with light blue of normal lesion, and we could easily recognized the cancer lesion. On the other hand, in a patient of chronic pancreatitis, the image of stenotic lesion in pancreatic duct was seen in light blue, and we could not recognize the different color between stenotic lesion and normal lesion.

Conclusion. In previous studies on the gastrointestinal tract and bronchial tree, cancer lesions appeared dark red when examined by the LIFE-GI system. In pancreatic duct, the cancer lesion was detected in dark red images, too. In near future, autofluorescence pancreatoscopy might become useful examination for the detection of cancer lesion of pancreatic duct.

THE EFFECT OF OBSTRUCTIVE JAUNDICE (OJ) ON PANCREATIC DAMAGE INDUCED BY DUCT OBSTRUCTION OF TOTAL PANCREAS
S. Iwasaki, S. Sumi, N. Ashizawa*, N. Hamamoto*, G. Xu, T. Urushihata, H. Watanabe, S. Yano, Y. Nio, Y. Kinoshita*, K. Tamura
First Department of Surgery and * Department of Internal Medicine II, Shimane Medical University, IZUMO, JAPAN.

Introduction. The obstruction of the pancreatic duct causes atrophy of pancreatic acini through apoptosis in rats. This study investigated the effect of OJ on this change. **Methods.** Three kinds of total pancreatic duct obstruction models were made in male Wistar rats; Group A: The duodenal end of the bilepancreatic duct (BPD) was ligated, Group B: In addition to group A, BPD was ligated at the hepatic hilus, Group C: In addition to group B, bile was drained into the duodenum (without OJ) and Group D: Sham operated. Rats were sacrificed on day 1, 2, 3, and 5 after the treatment. Body weight, diameter of the BPD, pancreas weight, dry/wet ratio of the pancreas, serum amylase and serum total bilirubin were measured. **Result.** Total bilirubin were higher in group A and B than group C and D throughout the study. Pancreatic wet weight/body weight increased in group A, B, and C until day 2. Then, in group B and C, it decreased to be lower than group D on day 5, whereas it did not decrease in group A. The dry/wet ratio decreased in group A, B and C. Serum amylase increased on day 1 in group A, B and C and, then decreased. On day 5, it was still elevated in group A than group C and D. BPD diameter continuously increased though the study in group A, B and C. However, on day 5, BPD was less dilated in group C than group A and B. Histological findings revealed that fibrosis around the interlobular ducts developed in group A and B but not in group C and D. Table shows the results on day 5 (value: mean $\pm$ SE. *: $p < 0.05$ vs Group C).

Table.	Group A	Group B	Group C	Group D
wet weight (g/kg BW)	4.4 $\pm$ 0.2*	3.1 $\pm$ 0.2	2.9 $\pm$ 0.2	3.6 $\pm$ 0.2
Amylase (IU/ml)	5607 $\pm$ 1171*	4252 $\pm$ 357*	2946 $\pm$ 568	3888 $\pm$ 613
BPD diameter(mm)	7.5 $\pm$ 0.6*	6.2 $\pm$ 0.2*	4.5 $\pm$ 0.4	0.5 $\pm$ 0.1

Conclusion. BPD diameter and histological findings suggested that the intraductal pressure was higher in the groups with OJ (group A and B). On the other hand, serum amylase suggested that the atrophy (presumably due to apoptosis) of the acini was disturbed by OJ. Therefore, OJ seems to inhibit self defense mechanism against pancreatic duct obstruction.

INSULINOMA OF PANCREAS -KOREAN EXPERIENCE
Hyuk-J. Jang*, Song C. Kim, Duck J. Han, In-K. Kim, Kun-C. Park
Department of Surgery, University of Ulsan College of Medicine & Asan Medical Center, Seoul, Korea

Introduction. Insulinoma is the most common functional endocrine tumor of pancreas even though its prevalence is relatively rare. In general, the tumor is a single and has a benign nature, so that the potential for surgical cure is very high. **Patients and Methods.** We retrospectively analyzed 50 including our own 14 patients who were diagnosed as insulinoma and underwent operation during a 25 year period from 1973 to 1997 at multiple centers in Korea. **Results.** There were 14 men and 36 women in this study. The mean age of the patients was 45 years (17~69 years). The most common clinical manifestation was loss of consciousness (86%) and all the patients had symptoms of Whipple's triad. The mean duration of symptoms before diagnosis was 46 months (1 month~20 years). The tumor can be localized in 37 patients (74%) preoperatively. The accuracy of tumor localization by ultrasonogram, CT scan, angiography and percutaneous transhepatic portal vein catheterization was 12%, 28%, 41% and 79%, retrospectively. Intraoperative ultrasonography was performed in six patients (12%). Multiple endocrine neoplasia type 1 (MEN1) was detected in three female patients (6%). Enucleation was performed in 20, pancreatic resection in 31 patients, among which segmental resection in 2, distal resection 20, subtotal resection (80%) in 2, near total and total resection one each and pancreaticoduodenectomy was performed in 5. Reoperation was done in three cases due to improper detection of primary tumor, diffuse islet hyperplasia, and low grade malignancy each. The tumors were located at head (38%), body (26%), tail (30%) or multiple sites (6%) of pancreas. The size of the tumor was 1.5cm (0.5-6cm). The incidence of malignancy was 10% (5 cases). Operative mortality occurred in one (2%) of the 50 patients, while major morbidity developed in 5 patients (10%) such as a pancreatic fistula in 4 and a gastrointestinal bleeding in one. Symptoms of hypoglycemia and laboratory values were normalized in all the patient after operation. **Conclusion.** Even though insulinoma is known to be a mostly benign and single lesion, preoperative and intraoperative suspicion and accurate localization are mandatory to rule out the multiplicity and malignancy for the control of this curable disease.

HYPERINSULINEMIC HYPOGLYCEMIA IN ADULTS WITH NESIDIOBLASTOSIS AND ISLET CELL HYPERPLASIA IN KOREA

Hyuk-J Jang*, Song C Kim, Hyun-K Lee, and Duck J Han
Department of Surgery and Pathology, University of Ulsan College of Medicine & Asan Medical Center, Seoul, Korea

Introduction Nesidioblastosis and islet-cell hyperplasia with hyperinsulinemic hypoglycemia is a primary childhood disease and reported rarely in adults. Nesidioblastosis has been defined as a diffuse islet cell hyperplasia accompanied with a differentiation of islets arising from the pancreatic ductal epithelium. **Patients and methods** We retrospectively evaluated ten cases of adult onset nesidioblastosis and one case of islet cell hyperplasia including our own 3 cases. **Results** There were 7 males and 3 females in nesidioblastosis and one female in islet-cell hyperplasia. The average age was 47 years (22 - 67years). The mean duration of hypoglycemic symptoms was 5months (7days - 84months). The common clinical manifestations were neuroglycopenic symptoms (100%) and adrenergic symptoms (80%) such as loss of consciousness, sweating, dizziness, abnormal behavior and confusion in descending order of frequency. The average fasting blood glucose level was 31mg/dl. Hyperinsulinemic hypoglycemia was confirmed during prolonged fasting test. In two patients a combination of a negative angiography and a lack of difference in insulin concentration gradient in THPVC would suggest nesidioblastosis preoperatively. Distal pancreatectomy (40%) was done in 1, subtotal pancreatectomy (70~85%) in 3, whipple's procedure (70%) in 2 and near total pancreatectomy (95%) in 1 patient. The surgical treatment resulted in the normalization of serum glucose levels and disappearance of hypoglycemic symptoms in 7 patients (63.7%). In remaining 4 patients (36.3%) one patient can tolerate without any medication and three patients were treated with somatostatin analogue, steroid, and diazoxide with somatostatin analogue each. **Conclusion** In nesidioblastosis preoperative suspicion and proper diagnostic tools and prudent operative diagnostic procedure will enhance the diagnostic accuracy. In diffuse islet cell hyperplasia, wide surgical excision (75%-85%) of pancreas will denote the best treatment option for the control of postoperative hyperinsulinism.

A STUDY ON USEFULNESS OF SERUM PANCREATIC ENZYMES MEASUREMENT IN SCREENING OF PANCREATIC STEATORRHEA

3rd Dept of Internal Medicine, Hiroshima University, School of Medicine
Asako Kaji, Teruo Nakamura, Naoko Yamada, Taku Watanabe
Yusuke Tando, Toshihiro Suda

Introduction. To measure fecal fat is time-consuming, unpleasant and complicated for screening test on diagnosis of steatorrhea in pancreatic insufficiency. So we studied whether or not serum pancreatic enzymes measurement, which is consisted of six kinds of pancreatic enzymes and PFD test, is useful for screening of steatorrhea.

Subjects and Methods Subjects were consisted of 73 normal controls and 22 pancreatic insufficiency patients with steatorrhea (fecal fat excretion > 5 g/day). We measured serum amylase (A), p-type amylase (p-amy), lipase (L), trypsin (T), phospholipase A2 (P), elastase 1 (E), and PFD test (500mg, 6hours), and obtained sensitivity and specificity for diagnosing steatorrhea. We judged mean $\pm 2SD$ as normal. The sensitivities and specificities were calculated from them.

Results. 1) For patients with steatorrhea, the sensitivities of PFD, p-amy, T, P, E, L and A were 85.7%, 81%, 78.9%, 73.3%, 66.7%, 60% and 13.6% respectively. 2) The specificities of p-amy, P, A, T, E, L and PFD test were 100%, 100%, 98.7%, 97.6%, 96.7%, 88.5% and 87.5%, respectively.

Conclusion. Although serum amylase measurement is not useful for screening test to diagnose pancreatic steatorrhea, serum p-amy measurement, judging from its simplicity, good sensitivity and specificity, is most useful test for screening of steatorrhea. In addition, the other pancreatic enzymes measurement except for serum amylase are also useful for screening of steatorrhea due to pancreatic insufficiency.

GENE EXPRESSION OF HCG β IN PANCREATIC CANCER AND CLINICAL USEFULNESS OF URINARY GONADOTROPIN PEPTIDE.

A.Jimi*, N.Eriguchi, H.Wakasugi, T.Shimazoe, A.Kono, A.Funakoshi
Department of Pathology & Surgery, Kurume University, Kurume, Department of Gastroenterology, National Kyushu Cancer Center, Fukuoka, Japan

Introduction. We have shown that urinary gonadotropin peptide (UGP), a catabolite of human chorionic gonadotropin β -subunit (hCG β), is a new tumor marker in pancreatic cancer patients and that it is clinically useful for diagnosis of pancreatic cancer and differential diagnosis of chronic pancreatitis. We examined gene expression and production of hCG β in the resected tumor tissue and cell lines of pancreatic cancer, and also compared with those of mutant p53 protein.

Materials and Methods. Total of 42 pancreatic cancer surgically resected were studied. Three human pancreatic cancer cell lines (KP-1N, KP-2 and KP-3N) were used for subcutaneous transplantation in nude mice. After 1 month urine was collected and tumor was excised. Xenografted tumors were immunostained for p53 and hCG β . Activities of hCG β in the culture media and UGP in the urine of the nude mice were measured. UGP was measured by an EIA kit (ELNAS) using a specific antibody (B2102). Gene expression of hCG β was evaluated by the RT-PCR followed by Southern blot hybridization. The prognosis of pancreatic cancer were evaluated by UGP and mutant p53.

Results. The UGP-positive rates were higher for poorly differentiated carcinoma cells (61.1-100%) than well differentiated cell types (33.3%), although the mutant p53 protein-positive rates (42.9%) did not depend on carcinoma cell differentiation. The culture media showed high hCG β activity and urinary UGP was detected in tumor bearing nude mice. Gene expression of hCG β was confirmed. The abnormal high levels of UGP, but not mutant p53 expression indicated the poor prognosis (< 6 months death) of the patients.

Conclusion. UGP is capable of serving as a non-invasive tumor marker that should be clinically useful in the diagnosis and the evaluation of prognosis of pancreatic cancer.

PALLIATIVE OPERATION AND INTRAOPERATIVE RADIATION FOR CANCER OF THE PANCREATIC HEAD

Y. Kakugawa*, Y. Yamanami, J. Mikuni, Y. Kamiyama, T. Fujiya, H. Ono, K. Sugawara, K. Ouchi.
Department of Surgery, Miyagi Cancer Center, Natori, Japan.

Introduction. Carcinoma of the pancreas still has a dismal prognosis. Because of the markedly improved safety of the pancreatic operation, pancreaticoduodenectomy (PD) could be used as a palliative procedure with or without intraoperative radiation therapy (IORT). However the benefits of a palliative operation and IORT for survival and quality of life (QOL) of patients with cancer of the head of the pancreas are not clear.

Patients and Method. Between January 1982 and December 1996, 13 patients received PD with positive margins and 32 patients underwent surgical bypass for the cancer of the head of the pancreas. Six of 13 patients undergoing PD and 14 of 32 patients undergoing surgical bypass were treated with IORT. Survival and hospital-free survival (HFS), as an indicator of QOL, were studied in these patients.

Results. Although there was no significant difference in the survival of patients with PD or surgical bypass (median survival of 9 month and 7 month, respectively), HFS for 3 month or longer was achieved in 84.6% of the patients with PD, which was significantly higher than that of the 53.1% in patients with surgical bypass (p<0.05). Among TNM stage III patients, the median survival of the surgical bypass with IORT was 10 month, while that of the bypass alone was 5 month (p<0.05). In addition, HFS of 3 month or longer was achieved in 83.3% of the patients who underwent bypass with IORT, but in only 25.0% of the patients who received surgery alone (p<0.01). The addition of IORT to palliative PD neither prolonged survival nor improved HFS.

Conclusion. These results show the beneficial effect of palliative PD on QOL, and the efficacy of IORT for both survival and QOL was demonstrated in cases with stage III patients who underwent surgical bypass. However, for patients subjected to palliative PD, IORT is not considered to be beneficial for either survival or QOL.

FUNCTION OF THE ACCESSORY PANCREATIC DUCT IN THE PANCREATOBILIARY MALJUNCTION

T. Kamisawa*, Y. Tu, N. Egawa, N. Sakaki, J. Ishiwata¹⁾

K. Tsuruta, A. Okamoto²⁾, H. Baba, M. Koike³⁾

Department of Internal Medicine¹⁾, Surgery²⁾, Pathology³⁾, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan

Introduction Patency of the accessory pancreatic duct (APD) in the usual pancreatic duct system is about 40% as determined by dye-injection endoscopic retrograde pancreatography (ERP). **Patients and Method** We examined the function of APD in 56 cases of the pancreatobiliary maljunction (PBM). Existence of APD was examined roentgenographically. We injected contrast medium containing indigocarmine through the catheter in the main pancreatic duct and examined the excretion of the dye from the minor duodenal papilla endoscopically. **Results** APD existed in 11 of 26 cases of the congenital choledochal cyst. Patency of APD was detected in 5 of 9 cases examined by dye-injection ERP. APD existed in 15 of 30 cases of PBM without biliary dilatation, and APD was patent 4 of 13 cases examined. There was no significant relationship between patency of APD and associated biliary carcinoma, but 5 cases of the congenital choledochal cyst with APD bigger than 2 mm in diameter had no biliary carcinoma. Amylase level of the bile in cases of PBM with patent APD was frequently lower than that of cases with nonpatent APD. **Conclusion** It is suggested that in cases of PBM with patent APD, the incidence of carcinogenesis of the biliary tract might be lower, as the reflex of the pancreatic juice to the bile duct might be reduced by the flow of pancreatic juice from the upper dorsal pancreatic duct into the duodenum via the minor duodenal papilla.

A NEW EMBRYOLOGIC HYPOTHESIS OF ANNULAR PANCREAS

T. Kamisawa*, Y. Tu, N. Egawa, N. Sakaki, J. Ishiwata¹⁾

A. Okamoto²⁾, H. Baba, M. Koike³⁾

Department of Internal Medicine¹⁾, Surgery²⁾, Pathology³⁾, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan

Introduction There are two major hypotheses concerning development of the annular pancreas from the ventral pancreatic anlage: adhesion of the right ventral anlage to the duodenal wall (Lecco's theory), and persistence of the left ventral anlage (Baldwin's theory) reported in 1910. Though each theory has some problems and can account for only a few types of annular pancreas, no new theories have recently been advanced.

Hypothesis We reported a new embryologic hypothesis of annular pancreas which can account for the developmental mechanism of three types of arrangement of annular ducts, by reference to Odger's model. In annular pancreas with annular duct opening to Wirsung's duct, the tip of the left ventral bud proximal to the bile duct becomes fixed to the duodenum during atrophy of the left ventral bud. The left bud persists and then forms the annulus during rotation of the duodenum, while the right ventral bud develops into the ventral pancreas. In annular pancreas with annular duct opening into the major duodenal papilla with absence of Wirsung's duct, annular pancreas develops in the same mechanism as above, but the ventral pancreas is hypoplastic. In annular pancreas with annular duct opening into the common bile duct without communication with Wirsung's duct, the tip of the left ventral bud distal to the bile duct adheres to the duodenum and forms the annulus.

EMBRYOLOGY OF THE PANCREATIC DUCT SYSTEM

T. Kamisawa*, Y. Tu, N. Egawa, N. Sakaki, J. Ishiwata¹⁾

A. Okamoto²⁾, H. Baba, M. Koike³⁾

Department of Internal Medicine¹⁾, Surgery²⁾, Pathology³⁾, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan

Introduction The human pancreatic duct system, the main pancreatic duct (MPD) and the accessory pancreatic duct (APD), is formed by fusion of the main drainage ducts of the ventral and dorsal pancreatic primordia. **Patients and Method** APD shows two different patterns in pancreatograms; long and short type. APD of the long type forms a straight line and joins MPD at the neck of the pancreas. APD of the short type joins MPD near its first inferior branch. Two hundred fifty-five pancreatograms of normal pancreatic head were reviewed. **Results** We found long inferior branches exceeding 2 cm from APD in 74.6% with long type, significantly oftener than 30.2% with the short type. Patency of APD of the long type was 74.5%, significantly greater than 36.2% in the short type. Immunohistochemically, we found MPD between the junction with APD and the neck portion of the autopsy pancreas in the short type lay within the ventral pancreas, characterized by pancreatic polypeptide rich islets. **Conclusion** The long type represents a persistent main duct of the dorsal primordium. The short type likely is formed by the proximal main duct of the dorsal primordium and its long inferior branch, with the main duct of the dorsal primordium at the point of connection with the main duct of the ventral primordium being obliterated and replaced by this additional communication.

THREE-DIMENSIONAL IMAGING OF INTRAPORTAL ENDOVASCULAR US FOR PANCREATIC CANCER

Tetsuya Kaneko, Akimasa Nakao

Department of Surgery II, Faculty of Medicine, University of Nagoya, Nagoya, Japan

Introduction. With recent progress of ultrasound technology, an intravascular ultrasound (IVUS) catheter was developed and intraportal endovascular ultrasonography (IPEUS) is now possible. IPEUS provides crisp, high-resolution, cross-sectional images perpendicular to the portal vein axis, and portal vein invasion is diagnosed as obliteration of an echogenic band of the portal vein wall. However, the rotational orientation and longitudinal extent of portal invasion are difficult to understand in terms of topographic anatomy of the portal vein. Three-dimensional (3-D) imaging of IPEUS has since facilitated the interpretation of the ultrasound scan.

Patients and Method. The 3-D imaging of IPEUS was constructed in 20 patients of pancreatic head cancer who underwent operation and IPEUS. IPEUS was performed with 8-French, 20-MHz IVUS catheter from the branch of the superior mesenteric vein. The IVUS catheter was withdrawn about 80 mm from the intrahepatic portion to the intrapancreatic portion at 1 mm/sec by a mechanical pull-back device. The 2-D imaging data were compiled in videotape and transferred to the workstation for 3-D imaging (NeraIVUS, Sc Image, Los Altos, CA). The frame acquisition rate was 30 frames/sec, and 3-D images were constructed by surface rendering.

Results. A longitudinal cut-open image was constructed and viewed from the various cut plane. The invasion area was depicted as a defect of the portal vein wall. In case of compression, portal vein wall was kept intact and anatomical relation between tumor and the portal vein wall was easy to understand. A longitudinal cut-open image also showed the confluence the splenic vein, hepatic artery, and lymph nodes along the portal vein simultaneously.

Conclusion. With the progress of computer technology, 2-D IVUS image was sampled in digital format after analog-to-digital conversion, and 3-D image could be constructed. Thus, 3-D IVUS images reflect the portal vein structure correctly because there is minimal distortion of the 3-D image. The 3-D IPEUS image delineated the longitudinal extent of invasion which was difficult to assess only by cross-sectional findings. The anatomical relationships defined by 3-D IPEUS provide important information for the surgeon planning the strategy of pancreatic resection without contrast agent.

DETECTION OF MICROMETASTASIS IN LYMPH NODES IN PATIENTS WITH NEGATIVE LYMPH NODE INVOLVEMENT BY EXTENDED OPERATION FOR PANCREATIC CANCER

K.Kanemistu, T.Hiraoka, T.Tsuji, K.Inoue, N.Kitamura
First Department of Surgery Kumamoto, University School of Medicine, Kumamoto, Japan

Introduction. The prognosis after resection for pancreatic cancer remains poor. Even if extended operation was performed, the results have not been shown to be superior to lesser procedure. Therefore, we examined micrometastasis in resected lymph nodes, especially in patients with negative lymph node involvement, to evaluate rationale of extended operation and necessity of Intraoperative Radiation Therapy (IORT) as adjuvant therapy.

Method and Material. Resected lymph nodes in patients with negative lymph node involvement by Hematoxylin Eosin (HE) staining following extended operation combined with IORT were examined by immunohistochemical staining of cytokeratin. Lymph nodes of 132 of the peripancreatic node and 107 of the paraaortic node were examined.

Result. Immunohistochemical cytokeratin staining was positive in 13 nodes of the 132 peripancreatic nodes and in 2 nodes of the 107 paraaortic nodes. Five of seven patients with negative lymph nodes by HE examination had micrometastasis in peripancreatic nodes, and two of the five patients were positive in the paraaortic nodes.

Conclusion. Five patients (71.4%) of seven with negative lymph nodes by HE examination had micrometastasis. This suggests that extended dissection of regional lymph nodes and IORT for advanced pancreatic cancer is necessary to control local recurrence, but its survival results is limited for hepatic metastases.

THREE DIMENSIONAL CT IN PATIENTS WITH PANCREATIC DISEASE

E. Karasawa, MD, A. Yamada, MD*, K. Takasaki, MD** and N. Hayashi, MD***

*Dept of Radiology, **Dept of Surgery, ***Dept of Internal Medicine, Institute of Gastroenterology, Tokyo Women's Medical College, Tokyo, Japan.

Introduction. Three-dimensional recognition is essential for the diagnosis and surgical treatment of pancreatic tumor. The clinical usefulness of new 3 dimensional CT, Shaded Volume Rendering (SVR) was evaluated in patients with pancreatic diseases.

Patients and Methods. 25 patients with pancreatic diseases were enrolled in this study. Helical CT (Xpress/SX; Toshiba) was used for the collection of 3D data with a slice thickness of 3mm, a table movement of 3-5mm, a reconstruction pitch of 1-2mm. Shaded Surface Display (SSD), Maximum Intensity Projection (MIP) and were made by 3D Processor of CT (Real-Render) and utilized high quality 3D W/S (X-tension, Toshiba). SVR was performed using new 3D W/S. A non-ionic contrast medium was administered intravenously (3-5ml/sec, total 120-150 ml). Delay time was 20 sec for arteries, 70 sec for the portal vein.

Results. Three-dimensional CT made it possible to demonstrate clear anatomical relationships between pancreatic tumor and the portal or splenic veins by intravenous contrast injection. SVR was superior to SSD for delineating vascular and bile ducts structures, but was inferior to cine MIP image of vessels in quality.

Conclusion. From these results, it is reasonable to conclude that these devices contributes considerably to the improvement of the 3D CT image of the pancreatic disease

A CASE OF INVASIVE DUCTAL CARCINOMA (T1 case) WITH UNIQUE FINDINGS ON PANCREATOGRAM AND COMPUTED TOMOGRAM ARTERIOGRAPHY

H.Kaneto*, T.Endo, K.Yamashita, S.Sasaki, Y.Arimura, S.Motoya H.Sakamoto, F.Itoh, K.Imai, K.Takashima, K.Koito, M.Sato
First Department of Internal Medicine, First Department of Surgery, Department of Radiology, Department of Pathology, Sapporo Medical University, Sapporo, Japan

Pancreatogram and computed tomogram (CT) has been crucial to make a diagnosis of the pancreatic carcinomas. It is well known that irregular stenosis or interruption of the main pancreatic duct (MPD) and avascular mass are the characteristic findings. However, here we report a T1 invasive ductal carcinoma which showed unique findings with pancreatogram and CT arteriography. Pancreatogram demonstrated mild stenosis due to a filling defect in the MPD, similar to intra-ductal papillary tumor. On the other hand, CT arteriography clearly showed an avascular mass surrounded with weaker enhanced area than normal pancreatic parenchyma, although this finding was not detected completely by conventional enhanced CT. It was proven by histologic analysis of surgical resected specimen that the filling defect was corresponded to the invasion of carcinoma into the MPD and not only the avascular mass but also the weaker enhanced area were equivalent to the carcinoma tissue. Since these findings are not common to the invasive ductal carcinoma, further analysis regarding the finding of CT arteriography and histological evaluation of small pancreatic cancer in a large-scale study is required.

COLOR DOPPLER IMAGING OF PANCREATIC TUMORS WITH A GALACTOSE-BASED CONTRAST AGENT

E. Karasawa, A. Yamada*, M. Tenma, T. Hatori, T. Imaizumi, K. Takasaki**, N. Hayashi***, M. Ohto****

*Dept of Radiology, **Dept of Surgery, ***Dept of Internal Medicine, Institute of Gastroenterology, Tokyo Women's Medical College, Tokyo, Japan. ****Research Center of Charged Particle Therapy, NIRS

Introduction

The purpose of this study was to evaluate the clinical usefulness of a galactose-based and transpulmonary sonographic contrast agent using color Doppler imaging for assessing tumor vascularity of pancreatic tumors.

Patients and Methods

10 patients with pancreatic tumors (two serous cystadenoma, two mucin producing adenocarcinoma, three ductal carcinoma, two non-functional islet cell tumor and one tumor forming pancreatitis) were enrolled in this study to evaluate detection of vascularity using intravenous contrast agent (300, 400mg/ml, Shering co.). A conventional color Doppler sonography system (3.75MHz, PRF 4-4.5KHz) was used.

Results

Blood signals of the pancreatic tumors were enhanced in 6 of 9 patients with pancreatic masses using this transpulmonary agent. The signal enhancement was negative in 3 and equivocal in one case. No severe adverse effect was ensued during and after this procedure.

Conclusion

A new monosaccharide intravenous, transpulmonary sonographic contrast agent may be useful in diagnosing hypervascular pancreatic tumor such as serous cystadenoma, islet cell tumor and tumor forming pancreatitis.

NIACIN ATTENUATES RAT CAERULEIN PANCREATITIS

J.Kashimura, T.Shimosegawa, M.Koizumi, T.Toyota.
Third Department of Internal Medicine, Tohoku University
School of Medicine, Sendai, Miyagi 980-77, Japan.

INTRODUCTION: NAD(nicotinamide adenine dinucleotide) is an essential substrate for the mitochondrial electron transport and intracellular ATP level. Oxidant and radiation are known to deplete intracellular NAD, resulting in the induction of cell damage. Depletion of NAD can be prevented by an addition of nicotinic acid (niacin). Because it has been reported that niacin-supplement improved lung injuries caused by paraquat or LPS (lipopolysaccharide), we anticipated that niacin treatment might attenuate acinar cell injuries during acute pancreatitis through the inhibition of NAD-depletion. To investigate this hypothesis, the present study was carried out to examine the effects of niacin on the rat caerulein-induced pancreatitis.

METHOD: Niacin (NA group) or saline (SA group) was i.p. injected 12hrs before the induction of pancreatitis. Pancreatitis was induced by single i.p. injection of caerulein at a dose of 50 µg/kg to conscious rats. Six hrs after the induction of pancreatitis, the rats were killed by decapitation and the NAD level of pancreatic tissue was determined. To evaluate the pancreatitis, serum amylase activity, edema index [pancreatic wet weight (mg) / body weight (g)] and histology of the pancreas were examined.

RESULTS: Administration of niacin to normal rats at a dose of 500mg/kg BW increased the pancreatic NAD level to $177 \pm 12\%$ ($P < 0.01$). In SA group, NAD level of pancreatic tissue was reduced significantly ($79.5 \pm 0.8\%$ of normal rats; $P < 0.01$), whereas the decrease was prevented in NA group rats ($101.3 \pm 2.8\%$ of normal rats). In addition, both the serum amylase (6487 ± 106 IU/ml vs 27676 ± 1636 IU/ml; $P < 0.01$) and edema index of NA group rats (4.59 ± 0.08 vs 9.39 ± 0.60 ; $P < 0.01$) were significantly lower than those of SA group rats, and the histological changes were more slight in the former.

CONCLUSION: Pretreatment of niacin attenuated rat caerulein-induced pancreatitis, probably by preventing the reduction in the pancreatic tissue NAD. The data suggest that niacin may be a potential therapeutic agent for acute pancreatitis.

PANCREATICO-JEJUNOSTOMY IN WHIPPLE OPERATION FOR PERIAMPULLARY CANCERS; A National Study in Taiwan

C-G Ker, H-Y Chen, C-C Juan, S-C YU*, C-S Su*, LC Ho*, P-W Lin*, FF Chou*, J-S Chen*, K-T Lee*, P-C Sheen*
Institute of Gastroenterology, Yuan General Hospital, Kaohsiung. *1 National Taiwan University Hospital, Taipei. *2 Veterans General Hospital, Taipei. *3 Chung-Sang Medical & Dentistry College Hospital, Taichong. *4 National Cheng Kung University Hospital, Tainan. *5 Kaohsiung Chang Gung Memorial Hospital, and *6 Kaohsiung Medical college Hospital, Kaohsiung, TAIWAN.

Introduction. The pancreatico-jejunostomy (P-J stomy) has been termed the "Achilles heel of the Whipple operation". The incidences of morbidity and mortality following P-J stomy depend largely on the integrity of the pancreatic anastomosis. The numerous reconstructive techniques devised in attempts to improve the safety of the P-J stomy have been reviewed recently.

Patients and Methods. There were 385 patients who underwent a standard or modified Whipple operation for periampullary cancers in seven teaching hospitals distributed in Taiwan. The anastomosis method for the residual pancreas and a limb of jejunum are mainly divided two groups Group I is end-to-end ($n=82, 21.30\%$) and Group II is end-to-side ($n=305, 78.70\%$).

Results. The incidence of leakage from the P-J stomy were noted 11 (13.41%) and 19 (6.27%) for the group I and II respectively ($P < 0.05$). Re-operation required for these complication were found in 2 and 5 patients of group I and II but all fail except two of group II. The total hospital mortality of group I and II were 5 (6.10%) and 19 (6.27%) respectively ($P > 0.05$).

Conclusion. A end-to-side, duct-to mucosa isolated Roux loop P-J stomy following pancreatoduodenectomy has a lower leak rate than the method of end-to-end. Whereas, the post-operative hospital mortality was of non-significant difference.

INHIBITORY EFFECTS OF VITAMIN D ANALOGUES ON PANCREATIC CANCER CELL LINES.

S. Kawa*, T. Nikaido, K. Yoshizawa, Y. Aoki, Y. Karasawa, K. Funhata, K. Kiyosawa.

The Second Department of Internal Medicine, Department of Obstetrics and Gynecology, Department of Laboratory Medicine, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390, Japan.

Introduction. Anti-proliferative activity of noncalcemic vitamin D₃ analogues, 22-oxa-calcitriol on pancreatic cancer cell lines was compared with that of calcitriol with analysis of vitamin D receptor (VDR) status and the G₁-phase cell cycle regulating factors.

Methods. Antiproliferative effects of both agents were compared by the MTT method and the measurement of the tumor size of xenograft inoculated into athymic mice. VDR contents by Scatchard analysis and mutational analysis of receptor cDNA were performed. G₁-phase cell cycle regulating factors were analyzed by Western blotting.

Results. (1) *In vitro*, 22-oxa-calcitriol and calcitriol markedly inhibited the proliferation (3 of 9 cell lines) and caused a G₁ phase cell cycle arrest by the appearance of numerous domes. (2) *In vivo*, 22-oxa-calcitriol inhibited the growth of BxPC-3 xenografts more significantly than calcitriol without inducing hypercalcemia. (3) Hs 766T, showing no response to either agent, had the second highest receptor contents with no abnormalities in its primary structure. (4) In the responsive cells, significant up-regulation of p21 and p27, a shift of retinoblastoma protein into the hypophosphorylated form, and suppression of kinase activity of cdk2 were observed after 24 hours of treatment. Significant down-regulation of cyclins, cdk5 and cdk inhibitors were observed after 7 days. In nonresponsive cells, no such changes were observed.

Conclusion. 22-oxa-calcitriol may provide a more useful tool for the chemotherapy of pancreatic cancer than calcitriol. In responsive cells, these agents up-regulate p21 and p27 as an early event, which in turn could block the G₁-S transition.

ROLE OF TGF-β1 AND MATRIX METALLOPROTEINASE ON THE HEALING PROCESS OF THE PANCREAS IN ARGinine-INDUCED PANCREATITIS RATS.

Y. Kihara, M. Tashiro, H. Nakamura, T. Yamaguchi, H. Yoshikawa and M. Otsuki*.

Third Department of Internal Medicine, University of Occupational and Environmental Health, Japan, School of Medicine, Kitakyushu, Japan

INTRODUCTION. In acute pancreatitis, pancreatic tissues are considered to restore almost completely if the primary causes or factors are eliminated. Transforming growth factor (TGF)-β and extracellular matrix (ECM) are known to play an important role on the process of wound healing of the pathological diseases. On the other hand, several matrix metalloproteinases (MMP) are known to degrade ECM. It is recognized therefore that tissue repair represents a balance between synthesis and degradation of ECM components. The aim of this study was to elucidate the role of TGF-β1, ECM and MMP in wound healing following arginine-induced acute pancreatitis.

METHOD. Acute pancreatitis was induced by intraperitoneal injection of L-arginine (500 mg/100 g body weight) in male Wistar rats weighing 150-160 g. Rats were killed by decapitation at 24, 36, 48, 60, 72 h, and 5 and 7 days after the injection. Expressions of TGF-β1, fibronectin, type I, type III and type IV collagen mRNA were determined by Northern transfer analysis and that of MMP-1 and MMP-2 mRNA was examined by RT-PCR. Immunoreactivity of fibronectin in the pancreas was assessed by using monoclonal antibodies against rat fibronectin.

RESULTS. TGF-β1 mRNA expression was detectable at 36 h, reached the peak value at 48 h. Type I and IV collagen mRNA expression was elevated at 36 h, whereas fibronectin and type III collagen mRNA expression was increased at 48 h. Fibronectin, type I, III and IV collagen reached the peak values at 60 h. Thereafter, expressions of these ECM mRNA gradually decreased, but remained elevated until 7 days. MMP-2 mRNA was significantly increased at 72 h, and reached the peak value at 5 days. MMP-1 mRNA levels did not alter. Marked depositions of fibronectin were observed in the interlobular and intralobular space at 72 h, but they disappeared at 7 days.

CONCLUSION. The peak value of TGF-β1 mRNA expression was followed by that of ECM mRNA expression. Furthermore, the increased level of MMP-2 transcript was followed by disappearance of deposition of fibronectin. These findings suggest that TGF-β1 plays an important role on the production of ECM and that ECM degrading proteases is involved in the healing process of acute pancreatitis.

GENE EXPRESSION OF SOMATOSTATIN RECEPTOR SUBTYPES IN HUMAN EXOCRINE PANCREATIC CANCER

First Department of Surgery^b and the Otsuka department of Clinical and Molecular Nutrition^a, School of Medicine, The University of Tokushima, Tokushima, Japan.

Toru Kikutsuji^a, Masamitsu Harada^a, Seiki Tashiro^b and Mitsuo Itakura^a

Introduction. The antiproliferative effects of somatostatin and its analogs mediated by somatostatin receptors have been suggested on human and rodent pancreatic cancer cell lines. The aim of this study is first to evaluate the gene expression of somatostatin receptor subtypes in human pancreatic cancer cell lines and cancer tissues, second to evaluate the antiproliferative effects of somatostatin analogs, and lastly to evaluate the effect of sstr-2 expression.

Methods. Gene expression of five somatostatin receptor subtypes (sstr-1~5) in eight human pancreatic cancer cell lines (MIA PaCa-2, Panc-1, PSN-1, FA-6, SUTT-2, BxPc-3, Capan-1, Capan-2) was first examined, using a reverse transcriptase polymerase chain reaction (RT-PCR) method. The same method was then applied to pancreatic cancer tissues and normal surrounding pancreatic tissues which were surgically resected in ten patients. Antiproliferative effects of somatostatin and its two analogs were examined with MTT assay for three human pancreatic cancer cell lines and hsstr-2A gene transfected NIH 3T3 fibroblasts.

Results. All cell lines, human pancreatic cancer and normal surrounding pancreatic tissues expressed mRNAs of more than two sstr subtypes. Six of eight cell lines expressed sstr-1, 2, and 5, and two cell lines expressed sstr-2 and 5. Seven of ten pancreatic cancer tissues expressed sstr-1 and six of ten pancreatic cancer tissues expressed sstr-3. sstr-5 was not detected except one case of pancreatic cancer tissue. Six of seven normal surrounding pancreatic tissues expressed sstr-1 and all cases expressed sstr-3. All cancer cell lines, pancreatic cancer tissues and normal surrounding pancreatic tissues expressed sstr-2. Somatostatin and its two analogs inhibited EGF stimulated pancreatic cancer cell proliferation. The maximal inhibition occurred in MIA PaCa-2 by 1 nM of RC-160 with an inhibition of up to 27±5.9%. The inhibition of cell proliferation occurred after stable expression of hsstr-2A in NIH 3T3 fibroblasts.

Conclusion. Based on the unexceptional expression of sstr-2 in all examined cell lines and pancreatic cancer tissues and the random expression of other sstr subtypes and the antiproliferative effect of somatostatin analogs to pancreatic cancer cell lines, somatostatin analogs to mediate the antiproliferative effects through sstr-2 could be potentially useful for the anti-cancer treatment of pancreatic cancers.

OXIDATIVE STRESS-INDUCED CHANGES IN RAT PANCREATIC ACINAR CELLS: INFLUENCE OF SMALL MOLECULE ANTIOXIDANTS

H. Kim, J.Y. Seo, K.H. Kim

Dept. of Pharmacology, Yonsei University College of Medicine, Seoul 120-752, Korea.

Introduction. Oxidative stress is regarded as a major factor in the pathogenesis of both acute and chronic pancreatitis. The mechanisms by which free radicals damage the acinar cells are not to be clarified. Present study aimed to determine an adequate model of oxidative stress by investigating the susceptibility of isolated rat pancreatic acinar cells to oxygen radicals and by exploring the potential of small molecule antioxidants to prevent such injury.

Method. Pancreatic acinar cells were isolated from male Sprague-Dawley rats, 180-200g, and exposed to oxygen radicals generated by iron/adenosine diphosphate for 30 min at 37°C. As oxidative indices, lipid peroxidation and cellular levels of superoxide dismutase (SOD), glutathione (GSH) and GSH peroxidase were determined. Small molecule antioxidants, ranging molecular weight, 163-536, such as rebamipide, allopurinol, N-acetylcysteine and β -carotene, were treated to the cells simultaneously with oxygen radical generating system.

Result. Small number of acinar cells in the reaction mixture were more susceptible to oxidative stress than large number of the cells in the mixture. Antioxidant defences within the acinar cells easily disturbed by oxidative stress; increase in lipid peroxidation, and decreases in cellular SOD, GSH and GSH peroxidase. Small molecule antioxidants similarly prevented these cellular alterations caused by oxidative stress even if they are reported to scavenge different oxygen radicals.

Conclusion. Present iron/adenosine diphosphate system could be used for the studies on the mechanism of oxidative stress-induced pancreatic diseases, and therapeutic approaches to pancreatic disorders using small molecule antioxidants capable of leaving the circulation and readily crossing cell membranes.

ROUTINE BILIARY SPHINCTEROTOMY (SPT) MAY NOT BE INDISPENSIBLE FOR ENDOSCOPIC PANCREATIC SPHINCTEROTOMY

M.H. Kim*, S.K. Lee, S.J. Myung, D.W. Seo, S.Y. Kim, K.N. Shim, Y.S. Kim, H.J. Kim, J.S. Kim, Y.I. Min, Dep. of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Introduction: It is generally accepted that biliary SPT is mandatory to avoid possible cholestasis and infection due to edema after pancreatic SPT (Cremer M. Endoscopy 23:171,1991). However, above claim on dual SPT has not been proven by prospective randomized study. The aim of our study is to determine whether cholangitis develops more frequently when the patients have not undergone concomitant biliary SPT during the endoscopic pancreatic SPT.

Patients/Methods: Sixty patients (M:F=38:22, 15 to 34 yrs) with non-alcoholic chronic calcifying pancreatitis were enrolled. The patients with jaundice (bilirubin >3 mg/dl), cholangitis, or parenchymal liver disease were excluded. The patients were randomly subjected either to dual SPT (group I: n=30) or to pancreatic SPT alone (group II: n=30). In group I, the patients with both dilated choledochus and elevated alkaline phosphatase were categorized as group IA and the patients with normal liver function as group IB regardless of the bile duct diameter. In group II, the patients were classified as group IIA and IIB according to the same standards.

Results:	Dual SPT		Pancreatic SPT alone	
	IA (n=8)	IB (n=22)	IIA (n=9)	IIB (n=21)
Cholangitis	0	1 (4.5)	5 (55.6)*	0
Hemorrhage	0	1 (4.5)	0	1 (4.8)
Pancreatitis	1 (12.5)	0	0	1 (4.8)

() indicates percents. *Significantly more frequent than other groups (p<0.05).

Conclusions: Our results suggest that dual SPT may be indicated only in patients who have both dilated choledochus and elevated ALP. It is because the prevalence of cholangitis is not different between patients with and without concomitant biliary SPT when the liver function is normal regardless of the diameter of choledochus. Routine biliary SPT may not be indispensable for pancreatic SPT.

THE ACUTE LUNG INJURY OF EDEMATOUS AND NECROTIZING PANCREATITIS IN RAT

KH Kim, CD Kim, HS Lee, SJ Lee, HJ Park, YT Jeon, HJ Chun, CW Song, SW Lee, SH Um, JH Choi, HS Ryu, JH Hyun.

Department of Internal Medicine, Institute of Digestive Disease and Nutrition, Korea University College of Medicine, Seoul, Korea

Introduction. About 60% of all deaths due to acute pancreatitis occur within the first 7 days of onset and associated with acute lung injuries include pulmonary infiltrates, pulmonary edema related to adult respiratory distress syndrome. But it is unclear whether the acute lung injury is related with severity of pancreatitis. In this study, we have evaluated the association between acute lung injury and severity of disease in experimental acute pancreatitis. **Methods.** Twenty one male S-D rat (200-250g Bwt) were used. There were three groups: control (group 1, n=7), edematous pancreatitis (group 2, n=7), and necrotizing pancreatitis (group 3, n=7). For inducing an edematous pancreatitis, rat received a 4 hour intravenous infusion of cerulein (5 μ g/kg/hr). For a necrotizing pancreatitis, rat received intraductal injection of taurocholate (5% 0.1ml/100g Bwt). After pancreatitis was induced, pancreas, lung and blood were prepared for biochemical and histologic changes each other. Bronchoalveolar lavage (BAL) was also taken. **Results.** The findings of BAL and histology of lung were as follows:

Group	pH	WBC (/mm ³)	Macroph. (%)	Lymph. (%)	Neutroph. (%)
Control	7.50	109	98	1	1
Edematous	7.50	123	92	5	3
Necrotizing	7.50	97	83	7	10

Group	Neutrophil infiltration	Intraalveolar hemorrhage	Interstitial edema	Alveolar membrane thickening
Control	-	-	-	-
Edematous	-	-	-	-
Necrotizing	++	++	+	-

Conclusion. These observations suggest that the lung injury was strongly associated with severity in acute pancreatitis and neutrophil may be capable of important role in the development of lung injury.

RELATIONSHIP OF PLEURAL EFFUSION WITH THE PROGNOSIS AND SEVERITY IN PATIENTS WITH ACUTE PANCREATITIS

KH Kim, CD Kim*, HS Lee, SJ Lee, HJ Park, YT Jeon, HJ Chun, CW Song, SW Lee, SH Um, JH Choi, HS Ryu, JH Hyun.

Department of Internal Medicine, Institute of Digestive Disease and Nutrition, Korea University College of Medicine, Seoul, Korea

Introduction. The presence of pleural effusion has been proposed as a marker for severe pancreatitis. There is a controversy about whether pleural effusion in acute pancreatitis is associated with more severe disease. The aim of this study was to clarify the association between pleural effusion and severity in patients with acute pancreatitis. **Methods.** We evaluated retrospectively for 216 patients (M:137, F:77) with acute pancreatitis who admitted to our hospital during last 5 years. The diagnosis of acute pancreatitis was based on the typical signs and symptoms, enzyme elevation, and radiological findings. APACHE II and Ranson score at admission were used for severity. The patients were subdivided into four etiological groups: alcohol, gallstones, idiopathic and others. **Results.** Pleural effusion was seen in 46(21.3%) of 216 of patients. Alcohol was the most common etiology (19/27.1%), followed by gallstones (15/32.6%), idiopathic (8/17.4%) and others (4/8.7%). The effusions were bilateral in 21(47.8%), left-sided in 19(39.2%), and right-sided in 6(13%). Results of relationship between the etiology and severity of acute pancreatitis with and without pleural effusion are as follows.

Etiology	With Effusion					Without Effusion				
	Ranson		APACHE II			Ranson		APACHE II		
	0-2	3-6	>7	0-7	>7	0-2	3-6	>7	0-7	>7
Alcohol	10	8	1	11	6	35	13	3	38	13
Gallstone	10	3	2	12	4	33	10	0	35	8
Idiopathic	7	1	0	2	3	36	6	0	34	8
Others	4	0	0	4	3	31	3	0	33	1
Total	31	12	3	34	12	135	32	3	140	30

Pleural effusion was independent of the etiology of the disease and the location was also not correlated with severity of pancreatitis. The pseudocyst developed in 8(17.4%) of 46 of patients with pleural effusion but in 12(7.1%) of 170 of patients without pleural effusion. The mortality was 4.7% in patients with pleural effusion and 4.4% in control, respectively. **Conclusion.** Pleural effusions are considered as a useful predictor of severity and negative parameter for the course of the acute pancreatitis.

THE EFFECT OF APOPTOSIS ON EXOCRINE PANCREATIC SECRETION IN RAT FED RAW SOYBEAN

KH Kim, CD Kim*, HS Lee, SJ Lee, HJ Park, YT Jeon, HJ Chun, CW Song, SW Lee, SH Um, JH Choi, HS Ryu, JH Hyun.

Department of Internal Medicine, Institute of Digestive Disease and Nutrition, Korea University College of Medicine, Seoul, Korea

Introduction. Pancreatic growth induced by feeding raw soybean rapidly regressed in size when the diet was changed to chow diet. The morphological changes of pancreas during involution indicate that cell death occurred by the process of apoptosis, but little is known about the pancreatic functional changes which accompany the morphological alterations. This study was designed to compare the response of pancreatic exocrine secretion according to the morphological changes during and after raw soybean feeding in the rat. **Methods.** Twenty eight male S-D rat(200-250g) were used. There were four groups fed differing diets as follows: group 1(control, n=7) were given chow diet, group 2(n=7) were given raw soybean diet for 2 week, group 3(n=7) were given raw soybean diet for 2 week and then chow diet for 1 week, group 4(n=7) were given raw soybean diet for 2 week and then chow diet for 2 weeks. Pancreatic juice was collected for 15 min. via PE-10 tube placed in the pancreatic duct. For a resting or CCK stimulated state, each rat received an intravenous infusion of 0.5 M NaCl (1.56 ml/hr) or CCK (50, 100 and 200 ng/kg/hr). Pancreas was prepared for histology after experiments. **Results.** Pancreatic weight was significantly heavier in rat fed soybean(group 2) compared with those fed chow diet and pancreatic exocrine function was also increased according to duration of raw soybean feeding(group 1). But enlarged pancreas induced by feeding raw soybean for 2 weeks rapidly regressed in weight after chow diet (group 3,4). Also pancreatic exocrine function was decreased after chow diet. But, there was no difference in the response of pancreatic exocrine secretion to exogenous CCK stimulation in all four groups. The histological results revealed that the pancreatic involution may be a form of programmed cell death, apoptosis. **Conclusion.** Pancreatic growth was associated with increased pancreatic exocrine function. Apoptosis during pancreatic involution did not disturb pancreatic exocrine function. In the rat fed raw soybean, the pancreatic response to exogenous CCK stimulation was not different from normal pancreas.

EFFECTIVENESS OF EARLY ENDOSCOPIC PROCEDURES ON THE DIAGNOSIS AND TREATMENT OF THE GALLSTONE PANCREATITIS

KH Kim, CD Kim*, HS Lee, SJ Lee, HJ Park, YT Jeon, HJ Chun, CW Song, SW Lee, SH Um, JH Choi, HS Ryu, JH Hyun.

Department of Internal Medicine, Institute of Digestive Disease and Nutrition, Korea University College of Medicine, Seoul, Korea

Introduction. Gallstone pancreatitis has showed higher mortality and morbidity rate as compared to other causes of pancreatitis, and the proper timing of endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy (EST) is still controversial. But recent several trials reveals that early ERCP/EST is safe procedure and can reduce mortality and complication rate in gallstone pancreatitis. **Methods.** To assess the safety and effectiveness of early ERCP/EST, we performed ERCP and EST, if necessary, in 52 cases of acute gallstone pancreatitis during recent 4 years. The diagnosis of gallstone pancreatitis was based on the typical signs and symptoms, enzyme elevation, and radiological findings. Ranson criteria at admission were used for severity. **Results.** Early ERCP group (in 72 hours) were 33 cases and delayed group were 19 cases. Early and delayed EST group were 22 and 17 cases, respectively. No statistically significant difference was found between early and delayed groups in blood chemistry and the severity of pancreatitis according to Ranson criteria. Duodenoscopic findings show normal papilla in 20 cases, papillary edema in 24 cases, and hemorrhagic and lacerated papilla in 8 cases. No remarkable complications according to ERCP or EST were noted. The hospital days of early ERCP/EST group were significantly shorter than delayed group. **Conclusion.** This result suggest that early endoscopic procedures on the diagnosis and treatment were considered as a safe and effective treatment modality in the gallstone pancreatitis.

CHARACTERISTICS OF MUCINOUS DUCTAL ECTASIA OF THE PANCREAS

KH Kim, CD Kim*, HS Lee, SJ Lee, HJ Park, YT Jeon, HJ Chun, CW Song, SW Lee, SH Um, JH Choi, HS Ryu, JH Hyun.

Department of Internal Medicine, Institute of Digestive Disease and Nutrition, Korea University College of Medicine, Seoul, Korea

Introduction. Mucinous ductal ectasia (MDE) is characterized by mucin producing tumor causing pancreatic ductal dilatation. This study attempted to clarify the clinical, radiographic and histological features of this disease. **Patients and Method.** We reviewed total twenty eight cases of mucinous ductal ectasia which were reported in Korean literatures including our eight cases during a 6-yr period. **Results.** They included twenty men and eight women, aged 40-79 years. All patients presented with an initial clinical diagnosis of acute or chronic pancreatitis, suspected cystic neoplasm of pancreas, or biliary obstruction. At endoscopic retrograde pancreatography, twenty six patients showed mucin secretion from orifice (92.9%), twenty five patients showed patulous ampullary orifice (89.3%), and twenty six patients showed mucinous filling defects with dilatation of main pancreatic duct (92.9%). Pathological examination showed fifteen intraductal papillary mucinous hyperplasias (53.6%), nine intraductal adenocarcinomas (32.1%), and four adenomas (14.3%). **Conclusion.** With increasing use of ERCP, a diagnosis of MDE should be made more frequently because intraductal mucus provides an important clue. MDE may be one of the most curable forms of malignant pancreatic tumor.

THE TOTAL ANTIOXIDANT STATUS IN EXPERIMENTAL PANCREATITIS

KH Kim, CD Kim*, HS Lee, SJ Lee, HJ Park, YT Jeon, HJ Chun, CW Song, SW Lee, SH Um, JH Choi, HS Ryu, JH Hyun.

Department of Internal Medicine, Institute of Digestive Disease and Nutrition, Korea University College of Medicine, Seoul, Korea

Introduction. For identify the tissue injury by oxygen free radical (OFR) in experimental pancreatitis, measurement of lipid peroxidation products has been used. However, the antioxidant defence interact to form as integrated system, therefore, it may be inappropriate to rely on measurement of a single component as an indicator of the functioning of the entire system. Recently, Total Antioxidant Status (TAS) is developed for evaluating the overall performance of the antioxidant system. This study was to assess whether TAS is a useful indicator for evaluating the role of OFR as pathogenesis of experimental pancreatitis. **Methods.** Twenty-one male S-D rat (200-250g B.wt) were used. There were three groups: Group 1(n=7, control), Group 2 (n=7, cerulein), and Group 3(n=7, taurocholate). Each rat received an iv infusion of cerulein(5µg/kg/hr) for 4 hours or intraductal taurocholate (5%, 0.1ml/100g B.wt) injection. After pancreatitis was induced, blood samples for biochemical changes including TAS (Randox Lab. Ltd, Crumlin, UK) and glutathion peroxidase (GPx) were taken. Pancreas was prepared for histology. **Results.** Edematous and necrotizing pancreatitis were induced by cerulein and taurocholate, respectively in rat. The biochemical changes including TAS and GPx were as follows:

Group (Gp)	TAS (mmol/L)	GPx (U/g Hb)
Control (CO)	1.13 ± 0.09	294.0 ± 39.1
Cerulein (CE)	0.83 ± 0.04*	29.7 ± 2.2*
Taurocholate (TC)	0.62 ± 0.10*	26.0 ± 1.9*

Gp	Pancreas wt (g)	Amylase (U/L)	AST (IU/L)	ALT (IU/L)	Total Bilirubin (mg/dl)	Alk. phosph. (IU/L)
CO	0.86±0.1	3146±5129	47.7±14.4	40.4±6.0	0.23±0.007	47.3±7.5
CE	1.81±0.5*	13457.1±3989.2*	172.1±56.2	56.9±9.0	0.67±0.02*	216±5.9
TC	2.24±0.4*	7880±1917.9*	84.3±7.92*	162.2±117.4*	0.24±0.005	113.0±12.6*

* p< 0.05 vs control

Conclusion. TAS may be a useful indicator as evidence of OFR reaction in the pathogenesis of experimental pancreatitis.

DIAGNOSTIC USEFULNESS OF FINE NEEDLE ASPIRATES (FNA) OF CYST FLUID IN THE DIFFERENTIAL DIAGNOSIS OF CYSTIC TUMORS OF PANCREAS

Y-T Kim*, JK Ryu, IA Park*, YB Yoon, CY Kim.

Department of Internal Medicine and Pathology*, Seoul National University College of Medicine, Liver Research Institute, Seoul, Korea.

Background: Serous cystadenoma(SCA) and mucinous cystic neoplasm(MCN) are the most common cystic neoplasms of the pancreas. It is very important to differentiate between these neoplasms because almost all of SCAs are benign but many of MCNs are malignant. Previously it has been shown that these tumors could be distinguished by radiologic studies or cytologic features and tumor markers in the cyst fluid. But there are significant rates of overlaps in their findings and sufficient epithelial cells could not be aspirated to be examined. So other preoperative confirmative diagnostic test should be developed to be able to determine whether the cystic tumors must be resected or not.

Aim: The purpose of this study is to examine whether mucin staining of FNA especially for background fluid material which is secreted from tumor cells can differentiate MCN from other cystic lesions.

Methods: Seventeen FNAs were obtained from 4 SCAs, 5 MCAs, 1 mucinous ductal ectasia, 2 papillary cystic tumors, 1 adenocarcinoma and 4 pseudocysts. Cytologic analysis was performed and mucicarmine staining was done to see whether mucin is contained in the cytoplasm of the cells or in the background fluid material aspirated from the cysts.

Results: Epithelial cells were observed in 7(58%) from 12 cystic tumors. But morphologic features of the epithelial cells could not allow definite characterization of cystic neoplasms. No mucicarmine positive cells were found in FNAs from cystic neoplasms. On the contrary, background fluid material was stained positively with mucicarmine in 4(80%) of 5 MCNs and in 1 of 1 adenocarcinoma but not in cases of SCAs, papillary cystic tumors and pseudocysts. **Conclusion:** Mucicarmine staining of FNA from cystic tumor of pancreas especially for background fluid material is very useful in the differential diagnosis between MCN and other cystic tumors.

PAPILLARY AND CYSTIC NEOPLASM OF THE PANCREAS IN KOREA

- OUR EXPERIENCE AND COLLECTIVE REVIEW -

Song C Kim*, Hyuk J Jang, and Duck J Han

Department of Surgery, University of Ulsan College of Medicine & Asan Medical Center, Seoul, Korea

Introduction. Papillary cystic neoplasm(PCN) of the pancreas has been known as a rare, low grade malignant tumor occurring chiefly in young women. PCN accounts for approximately 2% of exocrine neoplasm of the pancreas.

Patients and Method. We retrospectively reviewed 79 cases of Korean experience including our own 8 cases.

Results. Female was predominant(M:F = 4:75), and mean age was 27.5 years. Chief complaints were abdominal pain (50.0%) and palpable mass(44.9%). Average size of the tumor was 9.5cm(range 3cm - 20cm),and main location was tail or body & tail(70.5%). In 4 cases, local invasion to duodenum, spleen, colon, and portal vein were present. Distant hepatic and peritoneal metastasis was found in one case. Most patients were treated with pancreatico-duodenectomy, distal pancreatectomy or local excision. One patient with head lesion underwent Roux-en Y cystojejunostomy. After resection, there was no local recurrence in any case during mean follow up of 30month(range 1month-9years) save one patients who died from hepatic metastasis after 2 years.

Conclusion. We conclude that PCN of pancreas can be regarded as an indolent, slowly growing tumor having a good prognosis after complete resection, but close observation is needed because of its metastatic potential, although it is rare.

EFFECT OF MEK INHIBITOR AND PI 3-KINASE INHIBITOR ON THE PROLIFERATION OF K-RAS MUTATED PANCREATIC CELL LINES.

Y-T. Kim*, JK. Ryu, YB. Yoon, CY. Kim.

Department of Internal Medicine, Seoul National University College of Medicine, Liver Research Institute, Seoul, Korea.

Introduction. Mutations of K-ras are detected in 80-90% of human pancreatic cancers. So K-ras is believed to play a very important role in cellular proliferation of pancreatic cells. In many kinds of cells Ras transduces signals through Raf, MEK (Mitogen activated ERK activating Kinase), and ERK (Extracellular signal Regulated Kinase) in a low. Recently it is known that PI 3-kinase (Phosphatidylinositol 3-kinase) is also very important in mediating Ras signals and can regulate signals of proliferation. Though Ras is thought to be the most important protein in pancreatic cells, the down stream pathways involved in Ras signal is not known well in these cells.

Aims. The purpose of this study is to see whether ERK or PI3-kinase are important in mediating signals for the proliferation of Ras-mutated pancreatic cells.

Methods. Miapaca-1, Panc-1, and Capan-2 cell lines were incubated in complete media for 24 hours. Media was changed into serum-free DMEM and incubated for 6 hours. Then MEK inhibitor (PD98059) or PI 3-kinase inhibitor (wortmannin) were added at the concentration of 0, 5, 10, 20, 50 µM, or 0, 50, 100, 200, 500 nM respectively and cells were incubated for 2 hours. Then cells were stimulated with EGF or FBS (fetal bovine serum) for 48 hours and methyl ³H-thymidine was added. Degree of DNA synthesis were measured with β counter.

Results. In all cell lines DNA synthesis were suppressed by MEK inhibitor but not by PI 3-kinase inhibitor. One of the results using Miapaca-1 cells are presented below.

Radioactivity(CPM) of S phase fraction of Miapaca-1 cells.

inhibitor	PD98059					wortmannin				
concentration	0µM	5µM	10µM	20µM	50µM	0nM	50nM	100nM	200nM	500nM
CPM	8277	7036	3182	5680	2175	10608	12553	9734	10267	

Conclusion. Proliferation signal in K-ras mutated cell lines is transmitted through ERK pathway not through PI 3-kinase.

Essential Role of Endogenous Glucocorticoids on Apoptosis in Rat Pancreas

K. Kimura, T. Shimosegawa, R. Abe, A. Satoh, A. Masamune, M. Koizumi and T. Toyota

The Third Department of Internal Medicine, Tohoku University School of Medicine, Sendai, Miyagi, Japan

Introduction. We previously reported that activation of the hypothalamus-pituitary-adrenal axis may work for preventing the progress of acute pancreatitis. In order to further clarify the mechanism, we examined the role of endogenous glucocorticoids (GC) in pancreatic acinar cell death *in vivo* and *in vitro*.

Methods. The rats undergone adrenalectomy (ADX) or sham-operation (Sham ope) were investigated for apoptosis (APO) in the pancreas and in various other digestive organs. In addition, the occurrence of APO in the pancreas during caerulein (Cn)-pancreatitis was studied in these animals. Rat pancreatic acinar cells, AR42J cells, were used to investigate the direct effect of RU38486 (RU), a GC receptor antagonist, on the acinar cell APO.

Results. ADX caused increases in the labeling index of TUNEL only in the pancreas. Characteristic features of APO were confirmed in the TUNEL positive pancreatic acinar cells by the electron microscopy. In Cn-pancreatitis of ADX rats, the TUNEL labeled acinar nuclei increased remarkably with time after Cn-infusion. RU induced dose-dependently the APO of AR42J cells, and administration of GC blocked the occurrence of APO in these cells. In RU-treated AR42J cells, Ca^{2+} influx into the nuclei was shown by the confocal laser scanning microscope. Wild type p53 mRNA was expressed in RU-treated AR42J cells.

Conclusions. These results suggest the dependency of pancreatic acinar cells on endogenous GC for the survival. Endogenous GC may therefore work as a safeguard of acinar cells by decreasing their sensitivity for cell death during acute pancreatitis.

CLINICOPATHOLOGICAL STUDY OF NON-ALCOHOLIC, TUMOR-FORMING PANCREATITIS.

S. Kiriya, S. Nakano, I. Takeda, T. Kumada, Y. Sone, A. Miyata, A. Yamamoto, K. Hayasi, H. Simizu, A. Tamoto

Department of Gastroenterology, Ogaki Municipal Hospital

Introduction. Pathophysiology of tumor-forming pancreatitis, especially non-alcoholic, has not been enough known. In this study, tumor-forming pancreatitis was clinicopathologically investigated.

Patients & Method. In 7 patients with non-alcoholic, tumor-forming pancreatitis, operated because of difficulty in differential diagnosis from pancreatic cancer, clinical features, imaging examinations and pathohistological findings of the pancreas were retrospectively investigated. There were 3 men and 4 women, and the mean age was 56 ± 12.5 . Pathohistologically, the degree of intra- and interlobular fibrosis, infiltration of inflammatory cells, and disappearance of the acinar tissue was examined.

Results. 1. They had rarely an abdominal pain, characteristic of pancreatitis; only one had a lower abdominal pain. Three patients had an immunological abnormality; primary sclerosing cholangitis, ulcerative colitis, and Sjögren's syndrome.

2. Imaging diagnosis: Complete obstruction and localized stenosis of the main pancreatic duct by ERCP were observed in 6 patients and one, respectively. Enhanced CT failed to demonstrate central low density area, often characteristic for pancreatic cancer, in 5 of 7 patients.

3. Pathohistologically, the characteristic change was a remarkable infiltration of inflammatory cells in the pancreas rather than interlobular fibrosis with disappearance of the acinar tissue. Inflammatory cells, mainly composed of lymphocytes, infiltrated remarkably in four, and moderately in two patients.

Conclusion. Patients with tumor-forming pancreatitis had rarely typical complaints as pancreatitis, with complications of immunological diseases in some cases, and have been often difficult to make a differential diagnosis from pancreatic cancer. Non-alcoholic, tumor-forming pancreatitis is a special type of chronic inflammation of the pancreas, and in some cases, may be a localized involved pattern of chronic pancreatitis with diffuse narrowing of the main pancreatic duct, with remarkable infiltration of inflammatory cells, and suspected to be related closely to autoimmunity. However, further investigations should be done in more details.

SIGNIFICANCE OF PRESERVATION OF THE NERVE PLEXUS AROUND THE SUPERIOR MESENTERIC ARTERY IN RESECTION OF PANCREATIC CANCER

T. Kinoshita, M. Konishi, K. Inoue, M. Ryu.

Department of Surgical Oncology, National Cancer Center Hospital East, Chiba, Japan

Introduction. Because of the common mode of perineural invasion of pancreatic cancer, extensive clearance of the nerve plexus becomes popular in Japan. However quality of life of the patient who received complete removal of nerve plexus especially around the superior mesenteric artery (SMA) is miserable. Most of patients suffer from severe diarrhea and malnutrition. In resecting pancreatic cancer, right or left half of the nerve plexus around the SMA is usually preserved in our institution. Intraoperative radiation therapy (20Gy of electrons) is also applied after curative resection. This procedure and pylorus preserving pancreaticoduodenectomy gives acceptable quality of life of the patients.

Patients and Method. Twenty eight patients received pylorus preserving pancreaticoduodenectomy and 8 patients received distal pancreatectomy for cancer of the pancreas (usual ductal adenocarcinoma) with above mentioned preservation of the nerve plexus and with intraoperative radiation therapy (20Gy) from July 1, 1992 to December 31, 1997. Quality of life of these patients were analysed by the change of body weight, performance status, food intake and a control of diarrhea.

Result. All patients recover to the normal performance status, gain weight as before and can take foods as before within 6 months after operation. Diarrhea of the patients was well controlled by drugs in outpatient clinic. No patient needed readmission to control diarrhea and malnutrition.

Conclusion. These results indicate minimally acceptable quality of life after our way of radical resection of pancreatic cancer. Especially preservation of half of the nerve plexus can prevent uncontrollable diarrhea and malnutrition.

GROWTH INHIBITION OF HUMAN PANCREATIC CANCER CELL LINE, HUP-T1, BY ANTISENSE OLIGONUCLEOTIDES DIRECTED AGAINST K-RAS GENE

K. Kita*, S. Saito, C.Y. Monoka, K. Ohzawa, A. Watanabe.

Third Department of Internal Medicine, Toyama Medical and Pharmaceutical University, Toyama, Japan.

Introduction: The K-ras proto-oncogene is activated in more than 80% of pancreatic cancers, mostly with point mutations at codon 12.

The aim of this study was to investigate the inhibitory effect of antisense oligonucleotides (ASON) directed against the K-ras gene on the growth of pancreatic cancer cell line. We also tried to clarify the sensitive location as a target site for the antisense oligonucleotide.

Materials and Methods: We used a cultured cell line, HUP-T1, established from malignant ascites of a patient with poorly differentiated pancreatic adenocarcinoma, in our laboratory in 1983. This cell line had a mutated K-ras allele (GGT to GTT) at codon 12. We designed four kinds of the phosphorothioate ASON to target two different regions, i.e., A. codon 12 and B. AUG translational initiation codon of the human K-ras mRNA.

A-I) mutation-matched ASON-codon 12; targeting GTT mutated codon.

A-II) mutation-mismatched ASON-codon 12; targeting the wild codon.

B-I) ASON-AUG 1; targeting the AUG codon, with intron sequence.

B-II) ASON-AUG 2; targeting the AUG codon, without intron sequence.

Sense sequences of each target site were also synthesized as control.

Each oligonucleotide was transfected into cancer cells by the liposome-mediated technique. Cell growth activities were estimated by MTT colorimetric assay. The levels of K-ras p21 protein productions were determined using western blotting analysis.

Results: All ASON inhibited the transfected cell growth as compared with respective sense sequenced oligonucleotide. Mutation-matched ASON-codon 12 inhibited the cell growth and K-ras p21 protein expression strongly as compared with mutation-mismatched one and sense sequenced oligonucleotide.

Conclusions: ASON directed against the K-ras gene effectively inhibited the growth of pancreatic cancer cell line probably through the reduction of K-ras p21 protein levels. ASON-codon 12 targeted K-ras point mutation was more efficient than mutation-mismatched one. These results suggested that ASON directed against K-ras gene would be useful for pancreatic cancer therapy, and codon 12 of mutated K-ras gene is an attractive region for antisense approach.

SUPPRESSION OF INTRACELLULAR RESISTANCE FACTORS BY ADRIAMYCIN AUGMENTS HEAT-INDUCED APOPTOSIS VIA INTERLEUKIN-1 β -CONVERTING ENZYME ACTIVATION IN PANCREATIC CARCINOMA CELLS

D. KOBAYASHI¹, N. WATANABE^{1*}, H. SASAKI², T. OKAMOTO², N. TSUJII², T. SATO², N. YAMAUCHI², Y. NIITSU²

¹Department of Laboratory Diagnosis and ²Fourth Department of Internal Medicine, Sapporo Medical University, School of Medicine, Sapporo, Japan.

Introduction. Combination of heat and various anticancer drugs can have a synergistic antitumor effect in vitro and in vivo, though the mechanism is not clear. We have previously shown that endogenous tumor necrosis factor (enTNF) acts as an intracellular resistance factor to inhibit the cytotoxic effect of heat by scavenging oxygen free radicals via the induction of manganous superoxide dismutase (MnSOD). Consequently, we examined whether the suppression of these resistance factors by combining anticancer drugs and heat cause augmentation of heat-induced cytotoxicity in pancreatic carcinoma cells.

Materials and Methods. (1) The human pancreatic carcinoma cell line, PANC-1, constitutively expresses appreciable amounts of enTNF and also demonstrates heat resistance, was used in this study. (2) Heat sensitivity was measured by dye-uptake assay and clonogenic assay. (3) The expression of enTNF was measured by a indirect fluorescein antibody method using polyclonal anti-human TNF antibody, and intensity of cell fluorescence was measured by a Fluoroskan II. MnSOD activity was assayed by the nitroblue tetrazolium method. (4) Apoptosis was determined by DNA ladder formation using agarose gel electrophoresis.

Results. (1) After treatment of PANC-1 cells for 15 h with adriamycin (ADM), the expression of enTNF was decreased by 43%, and MnSOD activity was suppressed by 55%. (2) The cytotoxic effects by the treatment of PANC-1 cells with ADM followed by heat were greater than the sum of those observed with the agents administered individually. Heat induced apoptosis was also augmented by pretreatment with ADM.

(3) Furthermore, the specific interleukin-1 β -converting enzyme (ICE) inhibitor, Ac-YVAD-CMK, reversed the augmented cytotoxicity. **Conclusion.** These results indicate that heat-induced apoptosis via ICE-like proteases is augmented by ADM, and that the inhibition of intracellular resistance factors such as enTNF and MnSOD is important mechanism underlying this phenomenon.

(a) THE EXPERIMENTAL STUDY ABOUT THE SEVERITY OF ACUTE ALCOHOLIC PANCREATITIS

(b) Y. Kodo, T. Tanaka, T. Fujii, Y. Matsugu, K. Koide, Y. Miura, Y. Ichiba, K. Dohi.

(c) Dept. of Surgery II, Hiroshima University, Hiroshima, Japan

Introduction. We previously reported a model of acute alcoholic pancreatitis, however this model did not reach a severe state. We considered that this is because the pancreas in dogs, unlike that in humans, is not fixed to the retroperitoneum. In the present study, we utilized the previous dog model but with the pancreas fixed to the retroperitoneum, and investigated the effect of the fixation in an experimental model of severe acute alcoholic pancreatitis.

Methods. Adult dogs, weighing 9-15 kg, were used. A gastric fistula was prepared, and an 8 Fr tube was inserted into the greater pancreatic duct. Two weeks after the insertion, the duodenum was isolated 5 cm apart from the greater pancreatic duct on the anal side, followed by administration of ethanol (at 2.5 g/kg) into the gastric fistula (Group Ar, n=6). In a second group, fixation of the pancreas to the retroperitoneum in addition to the same treatment as in Group Ar was performed (Group Ar+F, n=6). In a third group, fixation of the pancreas to the retroperitoneum only was performed (Group F, n=6). In a control group, only laparotomy was performed (n=6).

Results. Group Ar represents the model that we have already reported and in this group, biochemical and histopathological findings obtained 36 hours after administration of ethanol demonstrated acute alcoholic pancreatitis, although the disease did not become severe. In Group Ar+F, lethal condition was noted 24 hours after administration of ethanol. Accordingly, in all groups in this present study, laparotomy was re-performed 24 hours after administration of ethanol. In Group Ar+F, serum amylase, lipase, elastase, ALT, LDH, and Cr levels 24 hours after ethanol administration were higher than before, whereas serum Ca and Po₂ levels were lower. In Group Ar+F histopathological examination revealed that hemorrhagic necrosis and infiltration of inflammatory cells were noted in the pancreas, and in addition, variable damage were noted in the lungs, liver, and kidneys. These findings were not noted in any of the remaining groups.

Conclusion. Fixation of the pancreas to the retroperitoneum was considered to be an important factor responsible for rendering acute alcoholic pancreatitis severe.

A DIFFERENT GASTRIC EMPTYING FUNCTION IN SOLID AND LIQUID MEALS AFTER PYLORUS PRESERVING PANCREATODUODENECTOMY

I. Kobayashi*, M. Miyachi, M. Kanai, M. Nagino, S. Kondo, J. Kamiya, M. Nakao*, N. Hayakawa*, Y. Nimura.

The first department of surgery, Nagoya University School of Medicine and *Nagoya University Hospital Pharmacy, and *Tokai Hospital, Nagoya, Japan

Introduction. Recently, pylorus preserving pancreatoduodenectomy (PPPD) has become one of the standard surgical procedures for benign or malignant periampullary lesions. Although transient gastric stasis immediately after PPPD has been a frequent complication, the cause remains unknown. Changes in gastric emptying (GE) function in solid and liquid meals were investigated in patients undergoing PPPD.

Patients and Methods. 14 patients underwent PPPD for periampullary malignancies (2 papillary, 5 bile duct, 7 pancreatic head cancers). The liquid phase and solid phase GE function were evaluated before and after surgery (mean: on the 38th postoperative day, range: the 27th to 53rd day). Two pharmacologic GE tests were used: acetaminophen test for liquid phase GE and the sulfamethizole capsule food test for solid phase GE. The absorption of the marker agents depends on the GE rate, a quick rise in the blood drug concentration suggests rapid GE.

Results. The solid phase GE was delayed significantly in the postoperative period. The peak sulfamethizole concentration was $3.58 \pm 1.40 \mu\text{g/ml}$ at 150 minutes preoperatively and $2.08 \pm 1.15 \mu\text{g/ml}$ at 180 minutes postoperatively. The differences in liquid phase GE were not significant. The preoperative and postoperative peak acetaminophen concentrations were $11.9 \pm 1.6 \mu\text{g/ml}$ and $10.4 \pm 2.8 \mu\text{g/ml}$ at 60 minutes.

Conclusions. Gastric function in the early postoperative period after PPPD is characterized by delayed solid phase emptying but good liquid phase emptying.

A New Ultrasound Imaging Method in the Abdominal Area: Harmonic Imaging without an Enhancing Agent in Disorders of the pancreas.

S. KOJIMA, H. GOTO, Y. HIROOKA, A. ITOH, S. HAYAKAWA, Y. WATANABE, Y. ISHIGURO, S. HASHIMOTO, T. HAYAKAWA*, Y. NAITOH**

*2nd Department of Internal Medicine and **Clinical Laboratory Medicine, Nagoya University School of Medicine, Nagoya, Japan, ***Department of Medical Biophysics.

Harmonic imaging has been developed to enhance the effect of the contrast medium by intensifying second harmonic components derived from the contrast medium and subtracting intrinsic signals from tissues. However, even without contrast medium, harmonic imaging is known to improve lateral resolution and the signal-to-noise ratio compared with conventional US. In this study, we evaluated the diagnostic usefulness of harmonic imaging without contrast medium in disorders of the pancreas. (**Subjects and methods**) The subjects were 79 patients with pancreas disorders who underwent harmonic imaging without contrast medium at our department between December, 1996 and November, 1997. They consisted of 79 pancreas disorders (26 with ductal cell carcinoma, 26 with mucin-producing tumor, 10 with mass-forming pancreatitis, 9 with pseudo cyst, 5 with serous cyst adenoma, and one patient with islet cell tumor, with solid and papillary tumor, with lymphoepithelial cyst). We compared for clinical usefulness between conventional US and Harmonic image. Comparative criteria were as follows. **Equal**, Images equal to conventional US, **Better**, Images with more clear delineation, **Excellent**, Succeeded in obtaining images not visible using conventional US. The apparatus used was HDI3000 (ATL, Bothell, Washington, USA). (**Result**) Seventy four (93.7%) cases of all 79 patients were judged as Better or Excellent. For each disorder, the patients who were judged as Better or Excellent were 24/26 (92.3%) ductal cell carcinoma, 26/26 (100%) mucin-producing tumor, 9/10 (90.0%) mass-forming pancreatitis, 8/9 (88.9%) pseudo cyst, 4/5 (80.0%) serous cyst adenoma, 3/3 (100%) others, respectively. (**Discussion**) Exact reasons for the above advantages provided by harmonic imaging are unclear. But it is believed that the major reason for the improved imaging characteristics is the reduction in overall haze and clutter in the harmonic image. In the pancreas disorders, because the masses were more clearly delineated by harmonic imaging, harmonic image may take the place of conventional US in screening examination in the near future. (**Conclusion**) Harmonic imaging without enhancing agents is a very useful and new diagnostic methods in the pancreatic disorders.

ASSESSMENT OF THE DIAGNOSTIC VALUE OF MRCP (MR Cholangiopancreatography) IN PANCREATIC DISEASE

H. Komoriyama, T. Okada, I. Tanaka, H. Ikezawa, K. Kanasugi, M. Hagiwara, E. Yamanouchi*

Department of Surgery, Department of Radiology*, St. Marianna University, Yokohama City Seibu Hospital, Yokohama, Japan.

Introduction. In recent years there have been advances in the application of MR to pancreatobiliary disease, and the images have been evaluated highly. We therefore conducted a comparative assessment of ERCP and MRCP images.

Patients and Method. The subjects were seventy patients suspected of pancreatic disease between January 1996 and December 1997 in whom both ERCP and MRCP were performed.

Results. There were 4 patients with pancreatobiliary maljunction, 9 with chronic pancreatitis, 16 with pancreatic cancer, etc. The pancreatic duct was visualized by MRCP, but the branches could not be identified. Pancreatic cysts were clearly defined. In pancreatobiliary maljunction, both the bile duct and the pancreatic duct could be clearly seen. The periphery of occluded pancreatic ducts could not be seen by ERCP, but were visualized by MRCP.

Conclusions. MRCP is less governed by the skill of the person performing it, and does not cause complications. Based on image quality, however, we do not consider it a better method of examination than ERCP.

EXPRESSION OF CYCLOOXYGENASE-2 (COX-2) IN PANCREATIC TUMORS.

T. Koshiba*, R. Hosotani, Y. Miyamoto, S. Nakajima, S. Tsuji, K. Fujimoto, J.-U. Lee, M. Wada, R. Doi, M. Imamura.

Department of Surgery and Surgical Basic Science, Kyoto University, Kyoto, Japan.

Introduction A considerable amount of evidence collected from several experimental systems and clinical studies with NSAIDs indicates that cyclooxygenase-2 (Cox-2) may play a major role in colorectal tumorigenesis. It has also been reported that expression of Cox-2 in colorectal carcinoma tissue and gastric carcinoma tissue was higher than normal mucosa. But little information about Cox-2 expression in pancreatic carcinoma is available. Expression of Cox-2 was investigated by means of both immunohistochemical analysis and immunoblot analysis in pancreatic tumors. **Patients and Methods** Samples of tumor tissue were obtained from patients with primary pancreatic tumors who underwent surgical operations at our department. Expression of Cox-2 was investigated by means of immunohistochemical analysis (anti-human Cox-2 mAb) in 50 invasive ductal adenocarcinomas (sDAC), 16 intraductal papillary-mucinous adenocarcinomas (malignant IPMT), 10 intraductal papillary-mucinous adenomas (benign IPMT) and 5 normal pancreatic tissues. Immunoblot analysis was performed in 5 cancer tissues and 5 pancreatic cancer cell lines. Immunostaining results were scored from 0 to 9 with regard to ratio of positive tumor cells and relative immunostaining intensity, and samples with the score more than 4 were regarded as positive immunostaining. **Results** 1) Immunoblot analysis showed that Cox-2 protein expression was detected as a single band corresponding to a molecular size of 70 kDa, which is compatible with Cox-2, and expression rate in pancreatic cancer tissues was 5/5 and that in cell lines was 2/5. 2) The staining for Cox-2 was mainly identified in the cytoplasm of cancer cells. Immuno-positive rate of DAC was 72% (36/50), malignant IPMT was 31% (5/16), benign IPMT was 0% (0/10) and that in normal pancreatic tissues was 0% (0/5). Immuno-positive rate of DAC was significantly higher than that in malignant IPMT and in normal pancreatic tissues (χ^2 test: $p = 0.0037$, $p = 0.0007$), and that malignant IPMT was significantly higher than that in benign IPMT ($p = 0.018$). 3) There was no significant correlation between expression of Cox-2 in DAC and prognosis of the patients or clinicopathological factors of the tumor, such as pTNM, clinical stage, and histological grade in UICC classification. **Conclusion** Cox-2 was expressed in 72% of invasive pancreatic ductal carcinomas and 31% of intraductal papillary-mucinous adenocarcinomas, but not in intraductal papillary-mucinous adenomas and normal pancreatic tissues. It was suggested that Cox-2 might be involved in the carcinogenesis of intraductal papillary-mucinous adenocarcinoma and invasive ductal adenocarcinomas.

MOLECULAR MECHANISMS OF PANCREATIC DUCT CARCINOGENESIS IN HAMSTERS

Y. Konishi*, M. Tsutsumi and T. Tsujiuchi
Department of Oncological Pathology, Cancer Center, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634, Japan

Adenocarcinoma of the pancreatic ducts is the fifth leading cause of cancer death in both U.S. and Japan. Development of the disease is clinically silent so that at the time of the diagnosis, the vast majority of cases are incurable with a very poor prognosis. Thus, prevention and early detection offer the only hopes for effective control of this deadly disease. The experimental model of pancreatic duct carcinomas by N-nitrosobis(2-hydroxypropyl)amine (BHP) and related nitrosamines in hamsters was first introduced by Dr. Krüger in 1974. During the past 20 years this model utilizing N-nitrosobis(2-oxopropyl)amine (BOP), the most potent of the propylnitrosamine family of pancreatic carcinogens, has been widely used for studies of duct carcinogenesis because the morphological, molecular, and histological features of the tumors closely resemble those of their human counterparts. However, the relatively long latent period prior to the appearance of pancreatic duct carcinomas has limited the application for studies of the mechanisms of pancreatic duct carcinogenesis and bioassays of modulation potential.

In this presentation, we would like to introduce our rapid production model for pancreatic duct adenocarcinomas and to report the mechanisms of pancreatic duct carcinogenesis so far elucidated in hamsters. This model incorporating the principle of selection by resistance to cytotoxicity demonstrated earlier for liver carcinogenesis. In this model, it is evident that a series of histogenetic steps are involved, leading from duct epithelial cell hyperplasia through atypical hyperplasia to intraductal carcinoma and invasive carcinoma. With regard to DNA alterations, K-ras mutations appear to be early events while p53 mutations generally occur in the tumor progression phase. Midkine and nm23/NDP kinase genes are over-expressed in invasive carcinomas and the induced cancer cells may show autocrine growth, secreting TGF- α and VEGF. Evidence of immortalization is provided by increased telomerase activity with shortened telomeres. The rapid production model of pancreatic duct carcinomas has not only provided a major stimulus to understanding induction mechanisms but should also serve as a bioassay to facilitate the identification of dietary risk factors and the search for appropriate chemopreventive and/or chemotherapeutic agents to help control this deadly disease.

TRANSCATHETER COIL EMBOLIZATION FOR INFERIOR PHRENIC ARTERY PSEUDOANEURYSM CAUSED BY ACUTE PANCREATITIS -A CASE REPORT-

S. Koyanagi¹⁾, R. Imamura¹⁾, K. Yasumori²⁾, H. Muranaka²⁾, K. Yosida³⁾, M. Furuyama³⁾, M. Saku³⁾, Y. Arita⁴⁾, M. Furukawa⁵⁾, B. Ando¹⁾

1); Department of Gastroenterology, 2); Radiology, 3); Surgery, National Kyushu Medical Center Hospital, Clinical Research Institute, Fukuoka, Japan. 4); The 3rd Department of Medicine, Faculty of Medicine, Kyushu University, Fukuoka, Japan. 5); Department of Medicine, Nakabaru Hospital, Fukuoka, Japan.

Introduction. Arterial pseudoaneurysm is one of the most catastrophic complication of pancreatitis. Interventional procedure has been reported as an effective and a safe treatment for such complication. Author report a rare case of inferior phrenic artery pseudoaneurysm secondary due to pancreatitis treated successfully with the transcatheter embolization. **Patient.** A 49-year-old alcohol abuse woman was admitted to our hospital for acute pancreatitis. Computed tomography (CT) showed an enhanced mass and a pseudocyst at the tail of the pancreas. Angiography revealed an inferior phrenic artery aneurysm. Transcatheter embolization using microcoils was performed superselectively via the left inferior phrenic artery through a microcatheter. After this procedure, the pseudoaneurysm was disappeared on CT. The pseudoaneurysm, however, was regrowth accompanying with increasing level of serum elastase I after a month later. Therefore, additional embolization was needed. **Result.** After the second embolization, the pseudoaneurysm on CT enlarged again concomitant with transient elevation of serum elastase I. However it disappeared spontaneously later. The patient has not been suffering from the symptoms of pancreatitis. **Conclusion** We experienced a rare case of left inferior phrenic artery pseudoaneurysm caused by acute pancreatitis. Transcatheter embolization was an effective and a safety treatment for the pseudoaneurysm of this case.

THE p53 AND p21 GENES TRANSDUCTION INTO PANCREATIC CANCER CELLS INHIBIT CELL GROWTH AND TELOMERASE ACTIVITY

M.Kusumoto, T.Ogawa, H.Ueno*, K.Mizumoto, N.Suehara, H.Nuyama, L.Chang, M.Tanaka

Departments of Surgery I and Cardiology*, Kyushu University Faculty of Medicine, Fukuoka, Japan

Introduction. The p53 tumor suppressor gene plays important roles in regulating the cell cycle and apoptosis. The p21 gene product is induced by wild type p53 and mediates the G₁ arrest of the cell cycle. While activation of telomerase has been detected in majority of human cancers, it remains unclear whether there is any linkage between the tumor suppressor genes and telomerase activity in cancer cells. In the studies presented here, we investigated the effects of p53 and p21 genes transduction into pancreatic cancer cells on cell growth, apoptosis, cell cycle, and telomerase activity.

Materials and Methods. The cell line used is a human pancreatic cancer cell line MIA PaCa-2, which exhibits a p53 gene mutation. The exponentially growing cells were incubated with PBS (mock), or infected at a moi of 100 with AdLacZ (control), Adp21 (p21), or Adp53 (p53) for one hour. The number of cells was counted, cell viability was assayed using propidium iodide (PI), and telomerase activity was measured by TRAP assay for four days. Transitions of the cell cycle were analyzed by flow cytometry.

Results. Overexpressions of the p53 and p21 proteins were confirmed by Western blot analysis after transduction of the genes. Growth of the cells transduced with the p21 gene were restricted to 46% of control and arrested at the G₁ phase. However, apoptotic changes were not prominent. Telomerase activity was reduced to 32% of control. The p53 gene transduction caused more severely cell growth inhibition (14%) and induced apoptosis. Flow cytometric analysis showed accumulation of apoptotic nuclear fragments (the subG₁ area of cell cycle) with the G₁ arrest. Moreover, telomerase activity was completely depressed to 2% of control.

Conclusion. Our results demonstrate that the p53 and p21 genes inhibit growth of human pancreatic cancer cells and the p53 gene induces apoptotic cell death. Telomerase activity can be used as a parameter of the anticancer effect and might be related to cell cycle and apoptosis.

MANOMETRY DATA DO NOT PREDICT CLINICAL RESULTS AFTER ENDOSCOPIC DRAINAGE OF THE MAIN PANCREATIC DUCT

R. Laugier, C. Renou.

Gastroenterology Department, University Hospital, Marseille, France.

Introduction : increased main pancreatic duct (MPD) pressure is frequently considered as a mechanism of pain during chronic pancreatitis (CP) either calcifying or obstructive. Nevertheless, MPD pressure has never been assessed at the end of endoscopic drainage procedures in painful CP or pancreas divisum (PD) as a predictive factor of clinical effectiveness.

Patients and method : out of our cases of painful CP or PD treated by endoscopic drainage, 13 patients (10 men, 3 women, mean age=45.1 years, range 18-67) with good clinical results after a long term follow-up (45 months) were studied manometrically. The major feature was a MPD stricture in all patients (CP 11 in cases, PD in 2 cases) which was calibrated with a 7F (2 cases) or a 12F (11 cases) stent during a mean time of 13.6 months (range 9-31). The pressure was simultaneously measured in the duodenum (zero level) and in the MPD thanks to a dual electronic pressure device. The pancreatoco-duodenal gradient (PDG) represented the difference between pressure in the MPD and in the duodenum.

Results : the mean PDG did not decrease after drainage (16.1 before, 15.2 mm Hg after). The 7 patients who had normal PDG (10.2 before and 5.9 mmHg after) had a complete disappearance of the MPD stenosis. In the 6 remaining patients who had an elevated PDG after drainage (24.7 before, 22.4 mmHg after), the MPD stricture persisted or was unchanged. Sex, age, aetiology, duration of stenting or follow-up and stent diameter was not different in the 2 groups.

Conclusion : a normal PDG after endoscopic drainage of the MPD was always associated with a good anatomical result, while an elevated PDG could not predict the clinical effectiveness of treatment.

LONG TERM FOLLOW UP OF PATIENTS WITH DILATED DUCTS AND NORMAL ENDOSCOPIC SPHINCTER OF ODDI MANOMETRY (SOM)

R. Laugier, C. Renou.

Gastroenterology Department, University Hospital, Marseille, France.

Background and aim . SOM has already been demonstrated to be efficient for indicating endoscopic sphincterotomy (ES) in case of sphincter of oddi dyskinesia, when the biliary or the pancreatoco-duodenal gradient is enhanced. So far, no demonstration exists as to know what to do when these gradients are normal although symptoms exist and ducts are dilated. Our aim was to validate in a retrospective study the abstention of ES when SOM was normal in those patients.

Patient and Method 13 patients (M/F : 4/9, age range 24-81, mean 52.4+/-19.1 years) were included in this study. All but two presented with pain episodes of either biliary or pancreatic type. Biological cholestasis was present in 2 patients. Mean diameter of the main bile duct (MBD) was 10.1+/-4.1 mm at ultrasonography. Five patients had been previously cholecystectomized and 5 had gallstones. Endoscopic retrograde cholangio-pancreatography demonstrated a MBD diameter of 10.9 mm without stones. As SOM was normal in all cases, we decided not to perform ES (plateau value, amplitude and frequency of contraction gradients).

Results all 13 patients were followed up during a mean of 42 months. Three out of the 5 patients with gallstones were cholecystectomized as recommended before SOM and one more although no stones were detected. During the follow up, we observed one episode evocative of angiocholitis without biological proof 37 months after SOM (follow up 62 months), one episode of atypical pain while another patient presented with repetitive pain relieved by oral trinitrine spray. The 10 remaining patients were totally pain free. None has necessitated a endoscopic or surgical papillotomy.

Conclusion SOM is interesting in case of biliary or pancreatic pain and dilated duct. When SOM appears normal it seems to be relevant not to perform ES although the ducts are dilated.

SERUM LEVELS OF OXYGEN FREE RADICALS IN PATIENTS WITH ACUTE PANCREATITIS

J. H. Lee*, J. B. Chung, K. W. Kim*, J. H. Seo, Y. H. Park, Y. M. Moon, J. K. Kang, I. S. Park.

Gastroenterology Department, Pharmacology Department* and Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Korea.

Introduction. The generation of oxygen-derived free radicals has been implicated in the pathogenesis of experimental pancreatitis. The aim of this study was to determine the role of oxygen-derived free radicals in patients with acute pancreatitis.

Patients and Method. The serum levels of lipid peroxide(LPO), myeloperoxidase(MPO) and C-reactive protein(CRP) were measured 13 patients with acute pancreatitis and 14 healthy volunteers as control subjects. The severity of acute pancreatitis was assessed by Atlanta Classification.

Results. The mean age of patients with acute pancreatitis and healthy volunteers were 53.6±15.9 and 32.5±7.6 years. The sex ratio(M:F) of the two groups were 11:2 and 10:4, respectively. The serum levels of LPO, MPO, amylase and CRP were as follows(table).

	Control (n=14)		Acute Pancreatitis (n=13)		p value
	Mild(n=8)	Severe(n=5)	Total		
amylase(I.U./dL)	141.9±179.3	374.7±252.4	423.0±253.1	393.3±243.1	0.005
CRP(mg/dL)	5.7±1.7	11.5±6.8	38.7±38.1	21.9±26.5	0.030
LPO(nmoI/mL)	2.7±1.2	7.5±4.1	20.1±16.1	12.3±11.7	0.005

Data are expressed as mean±SD. *p=0.068, *p=0.053

Conclusion. The serum levels of LPO and MPO were higher in patients with acute pancreatitis than control group. Among acute pancreatitis group, these levels were higher in severe pancreatitis than mild pancreatitis but no statistical significance was found.

NONIMAGING PARAMETERS PREDICTING RESECTABILITY IN PATIENTS WITH PANCREATIC CANCER

J.K. Lee*, I.K. Kang, K.T. Lee, J.C. Rhee.

Department of Internal Medicine, Sung Kyun Kwan University College of Medicine, Samsung Medical Center, Seoul, Korea

Introduction. Resection rates of pancreatic cancer remain low even among patients with operable in imaging studies such as ultrasonography, dynamic CT, angiography. The purpose of this study was to evaluate the relationship between nonimaging parameters and resectability in patients with pancreatic cancer.

Patients and Method. From 1995 to 1997, eighty-three patients with pancreatic cancer were evaluated retrospectively. 47 patients underwent curative resection. 36 patients received palliative operation (n = 19) or were not operated (n = 17) due to distant metastasis or definite angioinvasion. We analysed whether abdominal pain, back pain, anorexia, vomiting, weight loss, performance status, jaundice (bilirubin > 3 mg/dl), CEA (> 4 ng/dl), and CA19-9 (> 40 U/ml), CA19-9 (> 100 U/ml) were related to resectability.

Results. In univariate analysis, resectability was correlated with abdominal pain, back pain, vomiting, performance status, and CEA. In multivariate analysis, abdominal pain, performance status, and CEA were significantly associated with resectability.

Conclusion. Abdominal pain, poor performance status, and elevated CEA level are ominous predictable factors of resectability in patients with pancreatic cancer.

IMPACT OF REGIONAL PANCREATECTOMY IN PANCREAS CANCER

Jung-J Lee, Duck-J Han, Hyuck-J Jang, Song-C Kim*, Sung-G Lee, Kun-C Park

Department of Surgery, University of Ulsan College of Medicine & Asan Medical Center, Seoul, Korea

Introduction. Pancreatic adenocarcinoma is characterized by low resectability and poor long-term survival due to distant metastases and locally advanced disease which precludes curative resection, while regional pancreatectomy improves resection rates in a locally advanced lesion. However this procedure has been reported to involve high mortality and morbidity without improvement of long-term survival. We are going to analyze this procedure comparing with other pancreatectomy and non-resection procedures in patients with pancreas cancer. **Patients and Method.** From August 1989 to September 1997, 162 patients operated on for pancreas adenocarcinoma were grouped into non-regional pancreatectomy group (NRP, n=32), regional pancreatectomy group (RP, n=37), and non-resection group (NR, n=93). Their clinical features, morbidity and mortality, and risk factors for prognosis were analyzed retrospectively. **Results.** Out of 162, 69(42.6%) patients underwent resection. Operative procedures were pancreaticoduodenectomy in 22 patients, distal pancreatectomy in 9, total pancreatectomy in 1, and regional pancreatectomy in 37. Overall morbidity was 25.0% in NRP, and 40.5% in RP. However there was no mortality in both groups. One-year survival rate was 50.7% in NRP, 30.0% in RP, and 11.6% in NR (p < 0.05). In a same stage, namely stage III one-year survival rate was 38.9% in NRP, 26.9% in RP, and 14.9% in NR (p < 0.05). Interestingly, in a locally advanced lesion such as T3, one-year survival rate was 37.0% in RP and no survival in NRP regardless of nodal status (p < 0.05). Factors affecting prognosis were tumor size (p=0.013), lymph node status (p=0.022), and tumor stage (p=0.021). **Conclusion.** Regional pancreatectomy improved resectability and survival rate in a locally advanced lesion without significant additive risks of morbidity and mortality compared with the classical resection procedures.

MECHANISM OF CELL DEATH IN PANCREATITIS INDUCED BY PANCREATICOBILIARY DUCT OBSTRUCTION IN THE RAT

K.T. Lee*, J.K. Lee, J.C. Rhee

Department of Internal Medicine, Samsung Medical Center, Sung Kyun Kwan University College of Medicine, Seoul, Korea

Introduction. Gallstone is the most common cause of acute pancreatitis, but the mechanism of cell death in human and experimental pancreatitis remains poorly understood. The experimental models of pancreatitis induced by duct obstruction are particularly important because they closely resemble the mechanical events that occur during or after gallstone passage. Thus, this study was designed to determine the mechanism of cell death in the model of pancreatitis induced by pancreaticobiliary duct (PBD) ligation in rats.

Methods. Thirty five male Sprague-Dawley rats were divided into six groups; Group A, sham operated; Group B, PBD obstruction for 1 day; Group C, PBD obstruction for 2 days; Group D, PBD obstruction for 3 days; Group E, PBD obstruction for 5 days; and Group F, PBD obstruction for 7 days. In each rat, we evaluated the biochemical and morphological changes. Biochemical parameters were serum amylase, lipase, AST, ALT, alkaline phosphatase and total bilirubin. Morphological changes were shown by light microscopy, chromatin condensation and DNA breaks were assessed using Apoptag In Situ Apoptosis detection kit.

Results. The level of amylase and lipase peaked within 24 hours after PBD obstruction, and returned to baseline after 5 days despite persistent obstruction. Acinar cell deletion and proliferation of ductal-like cells were prominent after 3 days of PBD obstruction without an acute inflammatory response. Complete deletion of acinar cells and severe atrophic changes of pancreas with fibrosis were observed after 7 days of PBD obstruction. When the TUNEL technique was used, PBD ligation in rats was noted to induce apoptosis in a monophasic manner. Apoptosis reached peak level on day three, and then declined.

Conclusion. The experimental pancreatitis model induced by PBD ligation of rats was compatible with the mild form of gallstone pancreatitis. Apoptosis was the major mechanism of cell death after PBD obstruction in rats.

INTRADUCTAL PAPILLARY MUCINOUS TUMOR OF THE PANCREAS

In T Lee, Duck J Han, Song C Kim*, Hyuk J Jang, Sung G Lee

Department of Surgery, University of Ulsan College of Medicine & Asan Medical Center

Introduction. Intraductal papillary mucinous tumor (IPMT) is an uncommon and not well defined intraductal pancreatic tumor. This tumor illustrates an good example of precancerous lesion from benign epithelial dysplasia to carcinoma. We are going to characterize the IPMT as a premalignant condition in the patients operated on in our department.

Patients and Method. We retrospectively analyzed 20 IPMT patients admitted and confirmed histologically from August 1994 to December 1997 in our department.

Results. Male was predominant as the ratio of 3:1 and the mean age was 62 years (47-73). The symptoms in the descending order of frequency were: upper abdominal pain in 14(70%) with 4 months of symptom duration, weight loss in 4(10%), and no symptom in 2 cases. According to CT, MRI, ERCP, main pancreatic duct was involved in 20% and focal ductal branch in 80%. Surgical procedures were total pancreatectomy in 4, pancreaticoduodenectomy in 12, segmental resection of pancreas in 1, distal pancreatectomy in 1, and bypass in 2. Site of tumor was head in 60%, uncinate 5%, body 10%, tail 15%, and diffuse in 10%. In histology ductal epithelial hyperplasia was detected in 15%, hyperplasia associated with dysplasia 15%, hyperplasia or dysplasia associated with adenoma in 5% and 10% each, and cancerous change in 55%. Pancreatitis was associated in 48%. The size of the tumor was 7.9 cm in the cancerous lesion and 2.5cm in benign lesion. Post resection mortality and recurrence were not detected during follow up period (1-19mo).

Conclusion. Regarding the incidence of IPMT in our series, this lesion should be ruled out in every patients complaining the symptom of pancreatitis. Considering the existence of an adenoma-carcinoma sequence in IPMT, pancreatectomy including the removal of entire lesion should be considered for the control of this curable disease.

Growth inhibitory effects of a novel somatostatin analog (TT-232) on pancreatic cancer.

Li Li, R. Hosotani, M. Wada, T. Koshihara, K. Fujimoto, Y. Miyamoto, R. Doi, S. Tsuji, S. Nakajima, M. Imamura. Department of Surgery and Surgical Basic Science, Kyoto University, Kyoto 606-01, Japan.

Somatostatin, a natural tetradecapeptide, possesses antisecretory and antiproliferative activities on several tumor cell lines. In recent years, many somatostatin analogs have been developed as antiproliferative agents. The antiproliferative actions were reported to be mainly mediated through the type 2 somatostatin receptors (sstR). The sstR2 was a major type of receptor among sstRs in normal pancreas, whereas it was less exhibited in pancreatic cancer. This fact is thought to be the reason why the formerly developed somatostatin analogs exert some side effects before they show their antiproliferative effect on pancreatic cancer. In 1996, however, a novel somatostatin analog with a unique five-residue ring structure, TT-232, was reported to have tumor-selective antiproliferative activity without antisecretory activity (PNAS. USA, 93, 12515-12518, 1996). We obtained TT-232 (D-Phe-Cys-Tyr-D-Trp-Lys-Cys-Thr-NH₂) and RC-160 (D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Tip-NH₂) from Dr. Fujii (Faculty of Pharmaceutical Sciences of Kyoto University). In this study, we examined whether these agents have antiproliferative effects and receptor binding activity in vitro and anti-tumor effects in vivo using human pancreatic cancer cell lines. **Methods:** 1. PANC-1, AsPC-1, Capan-2, CFPAC-1 and MiaPaCa-2 cells were employed. The cells were plated in 24 multi-well plates. In the exponential phase of growth in monolayer, the cells were incubated with TT-232 and RC-160 for 48h. The cells in monolayer were measured by Coulter-counter to compare the antiproliferative effects among these agents. Furthermore, cell survival fraction assay was done for TT-232 to deny a simple toxic effect. 2. PANC-1 cells affected with 5 μ M TT-232 for 48h were subjected to FITC-TUNEL staining to detect fragmented DNA. 3. AsPC-1 cells (1.5×10^6) were subcutaneously implanted to nude mice with simultaneous intraperitoneal injection of 5 mg/kg TT-232 twice a day for 31 days. 4. Membrane fraction (50 μ g/50 μ L) was extracted from Mia PaCa-2 cells and react with 50pM [¹²⁵I]-DTPA-TT-232 50 μ L following addition of 50 μ L of TT-232 in 10^{-6} - 10^{-12} M to plot the receptor-binding inhibition curve. **Results:** 1. TT-232 inhibited the growth of all of four cell lines in a dose-dependent manner. The IC₅₀s were approximately 5, 10, 15, 15 and 20 μ M in PANC-1, MiaPaCa-2, Capan-2, AsPC-1, CFPAC-1 cells, respectively. RC-160 had no antiproliferative effects on these cell lines. 1-100 μ M of TT-232 did not affect the cell survival fraction, indicating that the antiproliferative activity of TT-232 was specific effect within the concentrations used in these studies. 2. Approximately 30% of 5 μ M TT-232 affected cells was positively stained after FITC-TUNEL method. 3. Administration of TT-232 for 31 days significantly inhibited the growth of subcutaneous tumors, resulted in decrease in tumor size to only 30% against the control. 4. TT-232 inhibited the binding of [¹²⁵I]-DTPA-TT-232 to membrane fractions in a dose-dependent manner. **Conclusions:** TT-232, a new somatostatin analog, inhibited the growth of human pancreatic cancer cell lines in a dose-dependent manner probably through the receptor mediated mechanism. Apoptosis was involved in the growth inhibition. TT-232 showed receptor-mediated antiproliferative activity in vitro, and showed the anti-tumor activity in vivo, suggesting that TT-232 may be useful in various clinical aspects.

Clinical controlled study of early ERCP and endoscopic treatment in the acute pancreatitis

Li Zhao-shen, Xu Guoming. Dept. of Gastroenterology, Changhai Hospital, the Second Military Medical University, Shanghai, (200433), China

Introduction. To evaluate the value and safety of early endoscopic retrograde cholangiopancreatography(ERCP). **Patients and Methods.** 126 patients with acute pancreatitis were randomized to divide into two groups. Sixty six patients with acute pancreatitis in the early ERCP group were under-went early ERCP and endoscopic therapy (within 3 - 10 days). 60 patients with acute pancreatitis were not treated by surgically, endoscopically and early ERCP in control group. The disappearance of the abdominal pain, decrease of serum amylase level, the mean days and cost of the hospitalization and complications were observed in all the patients of two groups. **Results.** ① In the early ERCP group, ERCP showed that in 54.5% of case with biliary tract disease, 4 cases with pancreatic stones, 4 cases of pancreatic divisum, 4 cases of larger diverticula of around the papilla, and 17 cases of normal. ② 33 cases with biliary tract disease were treated by endoscopy including papillosphincterotomy, endoscopic nasal biliary drainage and endoscopic dilatation of the accessory papilla, with no complications. ③ There were no significant differences in the decrease of serum amylase level and the cost of the hospitalization in early ERCP group and control group, but the days of the disappearance of abdominal pain and the hospitalization were significant shorter in the early ERCP group than in the control group ($p < 0.01$). **Conclusion.** It is more safe and effective that the patients with acute pancreatitis undergo early ERCP and endoscopic therapy, especially acute severe biliary pancreatitis.

INTEGRATED TRADITIONAL CHINESE AND WESTERN MEDICINE THERAPY IN THE MANAGEMENT OF SEVERE ACUTE PANCREATITIS

Li Gang, ChenHaiping, ShenHaigang, WangKaicheng, Dept.Surgery, HangzhouTCM Hospital, Hangzhou 310007, P.R.China

Severe acute pancreatitis (SAP) is a critical illness with high mortality rate often requiring surgical therapy. To achieve reduced mortality rates in patients with SAP, the pancreatic group of Hangzhou TCM Hospital have managed SAP using integrated traditional Chinese and Western medicine (ITCWM) therapy for 10 years. **Method:** Included in the routine ICU therapy and need for surgery, we use a herbal mixture made of 生大黄(*Rheum officinale* Baill), 厚朴(*Magnolia officinalis* Rehd, et Wils), 枳实(*Citrus aurantium* L), 丹参(*Salvia miltiorrhiza* Bge), 川芎(*Ligusticum chuan Xiong* Hort), 牛蒡(*Achyranthes bidentata* Bl), 蒲公英(*Taraxacum mongolicum* Hand). Mazz), 生山楂(*Gardenia jasminoides* Ellis) 红藤(*Sargentodoxa cuneata* Oliv. Rehd, et Wils). An intravenous catheter is inserted into the rectum about 20-30cm deep, and 500ml the mixture was instilled 4-6 a day. In addition, 100ml of the mixture was introduced through a nasogastric tube into the stomach 4-6 a day clamping the tube for 30min after installation. When intestinal paralysis, ileus and abdominal distension were improved, the therapy was changed to 100ml of the mixture twice a day until MODS improved. **Results:** total mortality rate is about 9%(3/33) and revised mortality rate is about 3%(2 patients with SAP died from MSOF on the day admission, one only was 5hr, and the other was 21hr.). SAP criteria of seventy consist of Ranson's early object signs >3, Clinical criteria of Bank and Wise >1, APACHE-II >8 and Balthazar's CT >C. **Conclusion:** The results seem to indicate that ITCWM therapy may reduce the mortality rate in the patients with SAP when used with other standard techniques. Mechanism of action of traditional Chinese medicine include facilitating intestinal paralysis and promoting bowel content excreted, making pancreatic juice and gall drainage, increasing living-organ and pancreas blood-perfusion as well as oxygen utilization, blocking ischemic reperfusion injury, resisting cytokine injury (TNF α , PAF, IL-1, 2, 6), protecting intestinal barrier and decreasing organisms translocation, maintain micro-ecological equilibrium in gut, confront endotoxin and endotoxaemia.

A Clinical Study of 23 Cases of Pancreatic Stone Diseases

Li Zhao-shen, Xu Guoming. Dept. of Gastroenterology, Changhai Hospital, Second Military Medical University, Shanghai, (200433) China

Introduction. To investigate the clinicopathologic feature of pancreatic stone disease.

Patients and methods. The medical records of patients with pancreatic stone disease between 1978 and 1996 at our hospital were reviewed. 23 patients were enrolled and by definition calcification at pancreas was found by plain film, ultrasonography, CT scans or ERCP.

Results. Of the 23 patients, including 9 males and 14 females aging from 10 to 74 years with a mean of 40.5 years. Alcohol was the major cause of pancreatic stone disease in 5 patients (16.7%). Others were related with biliary disease (common bile duct stone, cyst). Upper abdominal pain was the most frequent symptom in our cases. ERCP showed 95.5% of pancreatic stone were distributed in the main pancreatic duct, only one patient in accessory pancreatic duct size of the pancreatic stone was 0.5 - 1.5 cm, 0.5 - 1.0 cm in 18 cases, >1.0 cm in 5 cases. Pancreatic duct had dilated in 20 patients. The major complication in our patients was diabetes mellitus (13.0%).

Conclusion. The clinicopathologic feature of pancreatic stone diseases in our study were not similar with those of westerners, Japanese and Chinese in Taiwan.

Clinical study on somatostatin in prevention of hyperamylasemia and pancreatitis after ERCP

Li Zhaoshen, Xu Guoming. Dept. of Gastroenterology, Changhai Hospital, Second Military Medical University, Shanghai, (200433), China

Introduction. To study the preventive effect of somatostatin in the hyperamylasemia and pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP). **Patients and Methods.** 128 patients randomly chosen received either somatostatin (intravenously, 250 µg, at pre-ERCP and during 4 hours post-ERCP) or isotonic saline as placebo. The mean concentration of serum amylase at 4 hours and 24 hours after ERCP was measured in all patients, and the abdominal pain and pancreatitis after ERCP was also observed in all patients. **Results.** The mean concentration of serum amylase at 4 hours and 24 hours was 298 ± 33 U/L and 140 ± 156 U/L in preventive group, 380 ± 33 U/L and 240 ± 210 U/L in control group, 3 cases have occurred acute pancreatitis in control group, and only 1 case in preventive group after ERCP. The mean concentration of serum amylase and case number of happen pancreatitis after ERCP were significantly lower in preventive group than that of in control group ($P < 0.01$). **Conclusion.** It is concluded that somatostatin used pre and post-ERCP can prevent effectively hyperamylasemia and acute pancreatitis after ERCP.

USE OF INHIBITORS OF PHOSPHOLIPASE A2 IN TREATMENT OF CHRONIC RELAPSING PANCREATITIS.

G. Lukashovich*, N. Gubergnts, Y. Zagorenko, S. Kozhemyakin. Department of Internal Diseases No 1, Donetsk State Medical University, Donetsk, Ukraine.

Introduction. Chronic relapsing pancreatitis (CRP) is a common disease of digestive system. The results of the treatment are not always satisfactory. Taking into consideration significance of the phospholipase A2 at pathogenesis of CRP, we used inhibitors of this enzyme in complex treatment of the disease.

Patients and Methods. 110 patients suffering from CRP in the exacerbation stage were observed in our clinic. 30 of them received usual therapy with spasmolytics, cholinolytics, fermental drugs (group I), 50 of the patients received additionally protease inhibitors such as contrycal, etc (group II), 30 other patients apart from the basic therapy received inhibitors of phospholipase A2 — tetacin-calcium (EDTA) in the dose of 10 ml once a day in the course of 10-15 days (group III). 30 healthy persons were also observed.

Results. Stopping of the pain syndrome was more effective in the patients received EDTA, than in other groups. In the group III pain syndrome remained the same only in one case (3.3%), pain decreased at 21 patients (70.0%), pain ceased at 8 patients (26.7%). Administering tetacin-calcium treatment, authentic improvement of the functional state of pancreas was reached. This results in increase of debit part of amylase, trypsin and lipase in duodenal contents and also in increase of index of immune-reactive insulin in blood. The level of immune-reactive phospholipase A2 was increased before treatment in the patients of all groups. Only in the patients of group III this index had significantly decreased after the treatment. Patients of group III had the following in comparison to group II: decrease of blood level of Ig E and frequency of positive reactions to the pancreatic tissue as reaction of lymphocytes blast-transformation showed.

Conclusion. Inhibitor of phospholipase A2 tetacin-calcium (EDTA) is an effective remedy in the treatment of CRP

5-HYDROXYTRYPTAMINE (5-HT) RECEPTORS MEDIATE THE RELEASE AND ACTION OF SECRETIN ON PANCREATIC SECRETION IN RATS

P. Li, T.M. Chang, W.Y. Chey*.

Konar Center for Digestive and Liver Diseases, University of Rochester Medical Center, Rochester, NY.

5-HT₂ receptors are widely distributed in both enteric and enteropancreatic nervous system. Duodenal acidification results in the release of not only secretin, but also 5-HT. However, it has not been clarified whether or not 5-HT receptors (5-HTR) plays a role on the release and action of secretin. We investigated the effects of pindolol (PD) and 5HTP-DP (both are 5-HT₁R antagonists), Ketanserin (KT, 5-HT₂R antagonist) and ondansetron (OD, 5-HT₃R antagonist) on pancreatic exocrine secretion and the release of secretin in response to duodenal acidification in anesthetized rats. In addition, a possible cholinergic role on the action of KT and OD was also studied. **Methods:** rats were prepared with duodenal pancreaticobiliary cannulas as well as jugular venous catheters. HCl (0.03N) was infused intraduodenally (id) with or without iv atropine at 50 µg/kg and 25 µg/kg/h. Various 5-HTR antagonists were administered iv. Exogenous secretin (2.5, 5 and 10 pmol/kg/h) was given iv in some rats. Pancreatic juice was collected to measure volume and bicarbonate output, and immunoreactive secretin level in plasma was determined. **Results:** In basal state, all 5-HTR antagonists so studied did not significantly influence pancreatic secretion or plasma secretin level. Both pancreatic secretion and release of secretin induced by duodenal acidification were dose-dependently inhibited by KT (1-100 µg/kg) and OD (1-100 µg/kg), whereas PD (1 mg/kg) or 5HTP-DP (1 mg/kg) did not. Atropine failed to modify KT- or OD-inhibited release of secretin by duodenal acidification. KT and OD also suppressed pancreatic secretion in response to exogenous secretin at 2.5 and 5 pmol/kg/h, but not 10 pmol/kg/h. Atropine partially reversed KT (10 µg/kg)-inhibited pancreatic secretion in response to secretin ($36.4 \pm 10.1\%$, $67.7 \pm 13.0\%$ vs $54.1 \pm 16.3\%$, $104.5 \pm 24.7\%$). **Conclusions:** 5HT₁R and 5-HT₂R mediate duodenal acidification-stimulated release of secretin and action of secretin at physiological doses. Cholinergic pathway may mediate the regulation of secretin action by 5HT₂R

DOES THE PANCREATIC ENZYME CONTENT MODIFY THE OUTCOME OF ACUTE PANCREATITIS?

M.C.C. Machado, J.E.M. da Cunha*, A.M.M. Coelho, M.S. Kubrusly, M.Z. Salem, HW Pinotti.

Department of Gastroenterology, Surgical Division, São Paulo University Medical School - São Paulo, Brazil

Experimental studies demonstrate the crucial role of proteases in the pathogenesis of acute pancreatitis (AP). However is not known if the amount of pancreatic enzyme into the organ determines the severity of AP. Previous studies have shown that undernutrition reduces the mortality of acute experimental pancreatitis probably by decreasing pancreatic enzyme content. The present study was designed to assess the effect of acute reduction of pancreatic enzymatic content in the outcome of experimental AP.

METHODS: Acute pancreatitis was induced in rats by infusion of 2.5% sodium taurocholate into the pancreatic duct through a P50 catheter. Pulmonary injury secondary to AP was evaluated by using a morphometric technique (Weibel, 1990). Hepatic cellular damage was evaluated through the study of mitochondrial respiratory function (RCR, S4, and ADP/O ratio). Amylase, trypsin and volume of ascitic fluid were also analysed. Rats were divided in two groups: Group I (Control group) 52 rats without reduction of pancreatic enzymatic content, Group II (Experimental group) 54 rats submitted to reduction of pancreatic enzymes by intravenous administration of physiological doses of caerulein ($0.2 \mu\text{g K}^{-1} \text{h}^{-1}$ - for 3h). Subsets of 18 rats of the group I and 22 rats of group II were used to determine the 72h mortality.

RESULTS: Mortality in Group I was 56% and in Group II 23% ($p < 0.05$). Pulmonary interstitial edema in animals of Group I was equal to $262.5 \pm 10.4 \text{ mm}^3/\text{mm}^2$ and in Group II $134.38 \pm 10.4 \text{ mm}^3/\text{mm}^2$ ($p < 0.001$). RCR determined in animals of Group I was 3.26 ± 0.09 , S4 equal to 43.09 ± 1.22 and ADP/O ratio equal to 1.87 ± 0.01 . In animal of Group II the same measurements were respectively: RCR = 3.91 ± 0.09 , S4 = 30.99 ± 1.99 and ADP/O ratio = 1.95 ± 0.01 ($p < 0.05$). Amylase and trypsin contents in the ascitic fluid in animals of Group I were respectively $231 \pm 24 \text{ udl}$ and $40.32 \pm 5.19 \text{ udl}$. In animals of Group II the ascitic fluid amylase content was $80 \pm 10 \text{ udl}$ and trypsin $9.75 \pm 1.25 \text{ udl}$ ($p < 0.05$).

CONCLUSIONS: Reduction of pancreatic enzyme content reduces mortality, pulmonary lesions and hepatic damage in AP, suggesting that the pancreatic enzymatic content plays an important role in the outcome of experimental AP.

SURGICAL TREATMENT OF INSULINOMA. STUDY OF 59 CASES
M.C.C. Machado, J.E.M. da Cunha*, P. Herman, T. Bacchella, S. Penteado, E. Abdo, J. Jukemura, A. Montagnini, M.A.C. Machado, H. W. Pinotti
Department of Gastroenterology, Surgical Division, São Paulo University Medical School - São Paulo, Brazil.

BACKGROUND: One of the major problems associated with the management of insulinomas is their preoperative localization after the diagnosis has been made. The purpose of this study was to analyze the efficacy of preoperative localization of these tumors and the immediate and late results of their surgical treatment.

METHODS: Fifty-nine patients with hyperinsulinism were studied and the results of the diagnostic tools for tumor preoperative localization were compared with findings at surgical intervention. The influence of the type of surgical procedure on the immediate and late postoperative courses was studied.

RESULTS: Fifty-five of the 59 cases were benign lesions. Preoperative diagnosis was possible by US in 28.1% of the cases, by CT imaging in 25%, by combined selective celiac and mesenteric angiography in 54.1%, by EUS in 27.2% and by assay of portal plasma insulin levels in 94.4%. In 54/55 cases (98.2%) the tumors could be identified intraoperatively by palpation. By the addition of intraoperative US all lesions were identified. Twenty-nine enucleations and 32 resections were performed in the 55 patients with benign tumors. The five patients with malignant lesions were submitted to pancreatic resections. There was no mortality in this series. External pancreatic fistulas were the most frequent complications and all healed spontaneously. Late diabetes developed in three cases after distal pancreatic resection. Long term results were excellent in 98.1% of the benign cases. Only one of the patients with malignant tumors survived more than 5 years.

CONCLUSIONS: It is concluded that preoperative localization of insulinomas is not absolutely necessary and by combining preoperative palpation with intraoperative US, mainly at reoperations, most of the cases can be adequately dealt with. Tumor enucleation is the best choice for treatment of the benign lesions except those associated with type I multiple endocrine neoplasia.

LIVER DYSFUNCTION DURING ACUTE PANCREATITIS (AP) AND BENEFICIAL EFFECT OF NAFAMOSTAT MESILATE.

Marotta F.*, J. Rezakovic I., + Chui D.H., + Wu J., Tettamanzi D., Barbi G.

GI Serv., S. Anna Hosp., Como, Italy; + Neuroscience Dept., Changchun Univ., China; J Liver Unit Crespi, Milano, Italy.

Introduction: Hepatic cell injury with subcellular organelle damage has already been reported in the course of AP. The aim of this study was to make an assessment of hepatic energy parameters during AP while testing 2 potentially protective molecules.

Materials and Methods: Sprague-Dawley rats, were allocated into 4 groups: A) saline at 0.6ml/hr for 6 hours; B) saline + Caerulein 5µg/kg/hr for 6h; C) as B, + 5mg/kg body wt. Taxol s.c.; D) as B, + 10mg/kg/hr Nafamostat Mesilate (FUT-175) i.v. Six hours later rats were sacrificed and venous, arterial and liver tissue samples were used for biochemical work-up.

Results: As compared to B, either C and D treatments limited the increase of GOT and GPT level ($D > C$, $p < 0.05$). However, only FUT-175 prevented ($p < 0.05$) the hepatic energy metabolism failure (arterial pyruvate, lactate, pyruvate/lactate ratio, acetoacetate and acetoacetate/3-hydroxybutyrate ratio, tissue ATP, ADP, AMP, Total Adenine Nucleotide and Energy Charge). A time-course increase of Lysosomal Cathepsin B leakage and mitochondria MDH leakage was observed in liver tissue of B group ($p < 0.01$ vs control). Both treatments equally limited such phenomena ($p < 0.05$). However, at 180min FUT-175 proved to be better than Taxol ($p < 0.05$).

Conclusion: These data confirm the liver involvement during AP and suggest that microtubule stabilizers and, to a greater extent, low molecular weight protease inhibitors may protect the inner liver tissue function. Reduced portal inflow of activated pancreatic enzymes, together with intracellular stabilizing and free-radical scavenging actions are candidate mechanisms.

THERAPEUTIC STRATEGY FOR MUCIN-PRODUCING TUMOR OF THE PANCREAS

H. Maguchi, N. Yanagawa, M. Osanai, H. Itoh, Y. Sakurai, K. Takahashi, A. Katanuma, S. Watanabe, T. Fujii, M. Tanno, T. Obara, Y. Kohgo

Center for Gastroenterology, Teine-Keijinkai Hospital, Sapporo, Japan
Third Department of Internal Medicine, Asahikawa Medical College, Asahikawa, Japan

Introduction: Mucin-producing tumor of the pancreas (MPT) has been increasingly recognized as a new clinical entity in Japan. Histopathologically, for the most part, it consists of intraductal papillary adenocarcinoma and adenoma, although some cases are diagnosed as hyperplasia. It is clinically important to distinguish adenocarcinoma / adenoma from hyperplasia.

Patients and methods: From 1983 to 1997, we have encountered 111 MPT cases, including 43 operated cases (23 adenocarcinoma, 15 adenoma, 5 hyperplasia). Initially we evaluated the relationship between imaging findings and histology, and continued to examine the changes of imaging findings for followed up cases.

Results: We classified MPTs into main duct type and branch duct type. Branch duct type was overwhelmingly predominant, and almost all of the main duct type were malignant. The branch duct type cases with excrescent nodule of 6mm or more, dilated branch duct of 25mm or more and/or main duct of more than 7mm were all adenocarcinoma and adenoma.

There is no effective imaging modality to distinguish adenocarcinoma from adenoma. However, it is possible to distinguish adenoma or adenocarcinoma from hyperplasia. We are following up 61 cases of suspected hyperplasia in accordance with our diagnostic criteria. Out of 61 cases, we have followed up 53 cases for more than 1 year. Almost all of them have shown no progress in their images.

Conclusion: Adenoma or adenocarcinoma of the MPT suspected require surgery, but hyperplasia highly suspected can be followed up.

CYTOKINES ACTIVATION AND PROFILE DURING ACUTE PANCREATITIS (AP) IS RELATED TO ENDOTOXAEMIA AND EXTENT OF NECROSIS.

F. Marotta*, +Z.L. Li, § Y. Naito, G. Barbi.

GI Serv., S. Anna Hosp., Como, Italy; +Gastroenterol. Dept., Shianxi Prov. Hosp., Xian, China; § Sumitomo Memorial Hosp., Nagoya, Japan.

Introduction: Recently the role of cytokines as "acute phase response" mediators within the common pathway of inflammatory processes has been suggested. The aim of this study was to make a time-course assessment of some parameters of the cytokine cascade during AP of different severity.

Materials and Methods: In 205 Wistar rats, three models of AP were applied: A) Caerulein-induced (7µg/kg/h for 6h i.v.); B) as A, plus 10mg/kg lipopolysaccharide (LPS) i.p. injection 3h afterwards; C) 3% Na-taurocholate injection into the common bile duct. Saline and sham-operation were considered for control of A/B and C group, respectively. Sacrifices were made at 1, 3, 6, 9, 12, 48h plus observation until death for extra 25 C-group rats. Samples were withdrawn for: routine chemistry, TNF-α, IL-6, IL-8, Granulocyte Colony-Stimulating Factor (G-CSF) and endotoxin (Ex).

Results: As a whole, peak levels of each cytokine were significantly higher in AP rats ($C > B > A$) than in control ($p < 0.001$). Levels in C group were higher vs A and B groups ($p < 0.01$) and increased later on. TNF-α and Ex level were negligible and delayed in group A. IL-6 and IL-8 were correlated in B and C group ($r: 0.44$, $p < 0.05$). However, only IL-8 and G-CSF correlated with the prognosis (days of survival) in C group ($p < 0.05$). Ex, which showed a time-course increase, was related to TNF-α, G-CSF and IL-6 ($p < 0.05$) but only G-CSF significantly correlated with the extent of necrosis ($p < 0.05$).

Conclusion: These data suggest that the severity of AP is related to an earlier and more sustained increase of some cytokines. TNF-α seems to tailor IL-6 and G-CSF correlation with Ex and necrotic damage.

PATHOPHYSIOLOGY OF AMINO-ACID (AA) PROFILE DERANGEMENT FOLLOWING TOTAL PANCREATECTOMY (TP).

F. Marotta F*, J. R. Barreto, +C.C. Wu, G. Barbi. GI Service, S. Anna Hosp., Como, Italy; J. Cancer Center, Tokyo, Japan; + Dept. of Surg., Veterans Hosp., Taichung, Taiwan.

Introduction. TP alters AA metabolism via deranged protein digestion/absorption and the loss of pancreatic endocrine secretion followed by hyper-AA. This study aimed to clarify its pathophysiology. **Materials and Methods.** Mongrel dogs were divided into: A) esophago- and cholecysto-jejunosomy with TP+splenectomy; B) splenectomy, as sham operation. Jugular vein and femoral artery were cannulated for infusion and for biochemical studies (glucose, immuno-reactive glucagon (IRG), insulin (IRI) and AA) on day 1, 3 and 7 post-op. Endogenous glucose production (rate of appearance-RA-in mg/min/kg) was studied by i.v. infusion of 6-³H glucose (0.05μCi/kg/min) after a bolus injection of 5μCi/kg and then glucagon infusion (30ng/kg) was set up. Group A was given either continuous infusion of insulin 0.2 U/kg/day (A1), or nothing (A2).

Results. IRI level remained unchanged while IRG level dropped in group A ($p < 0.001$) being restored by exogenous administration. Glucose level and RA increased in A2 ($p < 0.01$), as compared to A1 and B groups on the 1st post-op. day. After 1 week A1 and A2 showed comparable values. I.V. Glucagon increased ($p < 0.05$) either RA and glucose level in A1 and B group. However, RA decreased ($p < 0.05$) in group A2 and no further P-glucose change occurred. Group A showed an increase ($p < 0.01$) of total AA throughout the study while glucagon administration caused a significant drop in all groups ($p < 0.05$). Selected AA (to be shown in detail) showed such changes and only in group A2 BCAA increased without any further effect by i.v. glucagon.

Conclusion. These data show that hyper-AA following TP is mainly due to glucogenic-, urea-cycle and system A-(alanin-preferring transport) -AA increase.

NAFAMOSTAT MESILATE IMPROVES ENERGY METABOLISM AND HEMORHEOLOGICAL DERANGEMENT OF THE PANCREATIC GRAFT SOON AFTER TRANSPLANTATION.

F. Marotta *, + P. Safran, J. Z.L. Li, J. N.X. Liao. GI Serv., S. Anna Hosp., Como, Italy; + Econum Lab., Villeneuve d'Ascq, France; J Gastroenterol. Dept., Shianxi Prov. Hosp., Xian, China.

Introduction. During pancreatic transplantation, ischemia/reperfusion phenomena. The aim of this study was to test an antiprotease, i.e. Nafamostat Mesilate (FUT-175) on the metabolic and hemorrheological parameters of the graft.

Materials and Methods. 160 syngeneic Wistar rats underwent pancreaticoduodenal transplantation. The overall cold ischemia time was within 1h and the operating time was within 3h. Rats were then allocated to 3 different perfusion media via the sup. mesenteric artery. A) 3cc of saline + heparin 150IU; B) 2cc of Eurocollins + saline 1cc +heparin 80 IU; C) FUT-175 1.0mg/ml in normal saline + heparin 80 IU; Sham operation group served as control. Rats were sacrificed at 1, 3, 6 and 12 h. Blood samples from the portal trunk served for: malate dehydrogenase (MDH), amylase and trypsin. Pancreatic micro-circulation of the graft (flow velocity, shear rate, n. of sticking leukocytes) was studied by a video camera-assisted microscope. Samples of the pancreas were also removed for: mitochondria studies and Adenine nucleotides assay. **Results.** A significant ($p < 0.01$) time-course increase of portal MDH, trypsin and amylase and a decrease of all energy metabolism parameters occurred in group A and B but not in C ($p < 0.01$). Mitochondrial fragility was partly preserved in group C ($p < 0.05$). Further, FUT-175 lessened the histological and microvascular score ($p < 0.05$).

Conclusion. These data suggest that FUT-175 employed as a perfusion medium of the graft allows a significant overall (subcellular, microvascular, metabolic and histological) preservation of the organ with a likely more adequate functional restoration.

PREVENTION OF GASTRIC ENERGY METABOLISM AND SUBCELLULAR DAMAGE DURING ACUTE PANCREATITIS (AP) BY THE ANTIOXIDANT BIONORMALIZER (BN).

F. Marotta, * P. Safran, D. Tettamanzi + Y. Naito, G. Barbi. GI Serv., S. Anna Hosp., Como, Italy; * Econum Lab., Villeneuve d'Ascq, France; + Sumitomo Mem. Hosp. Nagoya, Japan.

Introduction. Scanty reports have suggested that during AP, subcellular organelle fragility and impaired tissue energy occurs in the upper GI tract. Recently, a potent natural antioxidant, i.e. BN, has been developed. We studied the reported gastric mucosa failure during AP while testing BN on the very early cellular events.

Materials and Methods. Wistar rats were allocated into 4 groups which were given perorally a 5ml saline solution of: A) 1g BN; B) 15μg/kg Misoprostol. After one week of either treatment, a caerulein-induced AP model (5μg/kg/h for 6h) was applied to both groups. C and D groups represented AP without any drug and healthy control, respectively. Rats were then sacrificed. Half of the stomach was frozen in liquid nitrogen to assay energy metabolism parameters and the other half for subcellular studies and glutathione assay. **Results.** Gastric juice pH was unaffected during both treatments. As compared to D, gastric mucosa of B and C groups showed a significant time-course increase of Lysosomal Cathepsin B leakage, mitochondria MDH leakage and TBARS ($p < 0.01$) together with decreased energy charge and glutathione concentration ($p < 0.05$). BN, although unaffected the overall course of AP, totally prevented the above gastric mucosa metabolic failure ($p < 0.01$ vs B and C groups).

Conclusion. These data strengthen previous reports on metabolic GI tract derangement during AP and point out a lipid-peroxidation mechanism as a relevant pathophysiological basis. Such phenomena were prevented by an oral supplementation with a novel natural antioxidant which is not inactivated by gastric acidity.

MILD ASYMPTOMATIC PANCREATIC INSUFFICIENCY MAY HIDE A PLASMA FATTY ACID PROFILE ABNORMALITY.

F. Marotta, * Y. Naito, + P. Safran, D. Tettamanzi, G. Barbi. GI Service, S. Anna Hosp., Como, Italy; Sumitomo Memorial Hospital, Nagoya, Japan; + Econum, Villeneuve d'Ascq, France.

Introduction. The aim of this study was to assess plasma fatty acid profile in asymptomatic chronic pancreatitis patients (CP) while attempting its correlation with other clinical variables.

Patients and Methods. We studied 18 patients with ethanol-induced CP. As control, 15 age- and sex-matched healthy subjects were considered. Patients were not on vitamin- or enzyme-supplements for at least 3 months prior recruitment. Blood was withdrawn for: vitamin A, E, total lipid, Retinol Binding Protein, zinc, prealbumin and plasma fatty acids. Patients were put on a 3-day 80g fat diet and a 24h-stool collection was used for Near Infrared Reflectance Analysis (NIRA) (Esetek, Grottaferrata, Italy). At the entry, calorie intake was not statistically different between the groups, but fat intake was lower in CP ($p < 0.05$).

Results. Serum level of vitamin A, Retinol Binding Protein, total lipid and zinc were comparable between the groups. However, prealbumin and vitamin E were significantly lower in CP patients ($p < 0.05$). Linoleic acid (18:2) and arachidonic acid (20:3) were significantly lower in CP patients ($p < 0.01$). Mild steatorrhea was showed by NIRA assay in CP patients (less than 10g fat/24h). Only linoleic acid values correlated with vitamin E/total lipid ratio ($r: 0.44$, $p < 0.05$). The latter parameters showed a significant relationship with NIRA value ($r: 0.67$, $p < 0.01$).

Conclusion. These data suggest that in CP patients with mild insufficiency, in spite of normal routine biohumoral values, subtle plasma fatty acid changes take place. Such abnormalities are paralleled by low vitamin E/total lipid ratio and unrelated to steatorrhea. However, the latter two parameters appear to be somewhat interdependent.

EFFECTS OF EXPERIMENTAL PANCREATITIS-ASSOCIATED ASCITIC FLUIDS ON ENDOTHELIAL ACTIVATION

A. Masamune*, T. Shimosegawa, M. Koizumi, T. Toyota
Third Dept. of Internal Medicine, Tohoku University School of Medicine, Sendai 980-77 Japan

Introduction. Multiple organ failure (MOF) is the most serious complication in acute pancreatitis. We previously demonstrated enhanced expression of ICAM-1 in severe acute pancreatitis, suggesting the role of activated endothelium. In this study, we examined effects of ascitic fluids prepared from rats with experimental necrotizing pancreatitis on the (i) cytokine expression, (ii) vascular tone, and (iii) microthrombus formation in human umbilical vein endothelial cells (HUVEC).

Methods. Experimental necrotizing hemorrhagic pancreatitis was induced in male Wistar rats with sodium taurocholate. At 24 h later, the peritoneal exudates were collected, centrifuged and HUVEC were treated with the supernatants. We examined (i) expression of interleukin (IL)-6, IL-8 by enzyme-linked immunosorbent assay; (ii) induction of mRNA for these cytokines, endothelial isoform of nitric oxide synthase (eNOS), endothelin-1, platelet-derived growth factor-B (PDGF-B), tissue factor, thrombomodulin by reverse-transcription PCR or Northern analysis, (iii) activation of nuclear factor kappa B (NF- κ B), nuclear factor IL-6 (NF-IL6), cyclicAMP responsive element binding protein (CREB) by electrophoretic mobility shift assay.

Results. IL-6 and IL-8 expression in HUVEC was induced in a dose-dependent manner. Comparably pronounced mRNA expression for these cytokines, endothelin-1, PDGF-B, tissue factor was observed. In contrast, mRNA expression of eNOS and thrombomodulin was downregulated. NF- κ B, NF-IL6, and CREB were activated by the treatment, suggesting that ascitic fluids contain soluble factors transcriptionally activating the endothelium.

Conclusion. Our results suggest that endothelial activation such as cytokine expression, vascular contraction, and microthrombus formation may play roles in the pathogenesis of acute pancreatitis.

SPONTANEOUS SECRETION OF NEWLY DISCOVERED LUMINAL CCK-RELEASING PEPTIDE (LCRF) IN CONSCIOUS RATS

M. Masuda, K. Miyasaka*, S. Kanai, K. Tateishi, A. Funakoshi.
Dept. Clin. Physiol., Tokyo Metropolitan Inst. Gerontol., Tokyo, 1st Dept. Biochem. School of Medicine, Fukuoka Univ., Fukuoka, Div. Gastroenterol. Natl. Kyushu Ca Ctr. Fukuoka, Japan.

Introduction. Studies in rats showed that diversion of bile-pancreatic juice (BPJ-D) from the small intestine strongly stimulated pancreatic enzyme secretion (luminal feedback regulation by protease). LCRF, a novel 8136 dalton peptide purified from rat intestinal secretion is a putative intraluminal regulator of CCK secretion. We have established a RIA for LCRF. We examined whether LCRF secretion was regulated by cholinergic regulation or inhibited by somatostatin, a potent inhibitor of CCK release and pancreatic secretion, in conscious rats. **Methods.** Male Wistar rats (300-330g) were prepared with cannulae draining BPJ separately, and with a duodenal and a right jugular vein cannulae. Rats were placed in restraint cages and experiments were conducted 4 days after the operation without anesthesia. After 1.5-h basal collection with BPJ return, BPJ was diverted and NaHCO₃ was infused instead (1ml/h). The changes in pancreatic secretion of fluid and protein were monitored for 4-h. Intravenous infusion of somatostatin-14 (2 nmol/kg/h) or atropine (100 μ g/kg/h) was started at the beginning of BPJ-D or 1-h before BPJ-D. The rats were sacrificed before and 2.4-h after BPJ-D, and the plasma CCK was measured by RIA using OAL-656 antibody. The luminal content of LCRF in the small intestinal lumen (proximal 20 cm) was measured by RIA.

Results. BPJ-D significantly increased pancreatic secretion and LCRF content in the lumen. The plasma levels of CCK also increased significantly paralleling the changes in protein secretion. Atropine did not affect plasma CCK, pancreatic secretion or LCRF content significantly. Intravenous infusion of somatostatin significantly decreased responses of protein secretion and CCK release to BPJ-D, while luminal content of LCRF was not affected. **Conclusions.** Secretion of LCRF was not inhibited by atropine or somatostatin. These results are compatible with our original proposal (AJP-G, 1989) that luminal CCK releasing peptide might be spontaneously secreted and luminal protease (trypsin) regulated its CCK-releasing activity.

LOCAL STAGING OF PANCREATIC CANCER: EVALUATION WITH THIN-SECTION HELICAL CT

S. Matsumoto, Y. Yasunari, H. Kiyosue, H. Hata, Y. Hon, H. Mon
Radiology Department, Oita Medical University, Oita, Japan

Introduction. The accurate staging of pancreatic cancer is mandatory in the preoperative status. Helical CT allows for detailed images of pancreas and peripancreatic structures, however there are few reports concerning the staging of pancreatic cancer on helical CT. The purpose of this study was to elucidate the utility of thin-section helical CT for local staging of pancreatic cancer.

Patients and Method.

Twenty patients who underwent surgery and pathologically confirmed pancreatic cancer were included in this study subjects. These patients prospectively underwent dynamic thin-section helical CT (5 mm slice-thickness, 5 mm/sec table speed, 2.5 mm reconstruction). CT findings were interpreted by three radiologists according to the *General Rules for the Study of Pancreatic Cancer* established by Japan Pancreas Society, i.e., the size, serosal (anterior) and retroperitoneal (posterior) extension, arterial and portal invasion, duodenal invasion, bile ducts invasion, extrapancreatic nerve plexus invasion. The accuracy of CT staging was determined by the correlation with surgical and pathological findings.

Results. Tumors were detected in all patients on CT, but the size tended to be smaller at CT than at pathology. The accuracy of helical CT was 85% for serosal invasion, 85% for retroperitoneal extension, 100% for arterial invasion, 92% for portal invasion, 94% for duodenal invasion, 88% for bile ducts invasion, 90% for extrapancreatic nerve plexus invasion. The evaluation of peripancreatic veins such as inferior pancreaticoduodenal vein was useful for determining the duodenal invasion or extrapancreatic nerve plexus invasion.

Conclusion. Thin-section helical CT is an important tool for preoperatively determining the local staging of pancreatic cancer.

PANCREATIC FIBROSIS INDUCED CHRONIC ADMINISTRATION OF A SUPEROXIDE DISMUTASE INHIBITOR IN RATS

Naoki Matsumura, Koji Ochi, Motohiro Yokoyama, Takaaki Mizushima, Mitsuko Ichimura, Hideo Harada

Department of Laboratory Medicine, Okayama University Medical School, Okayama, Japan

Introduction. Reportedly, free radicals induce fibrosis in various organs, but such reports are scarce for pancreas. Our preliminary study revealed that a rise in lipid peroxide concentration with a fall in SOD in pancreatic tissue was induced at 3 h after a single intraperitoneal (IP) injection of diethyldithiocarbamate (DDC), a known superoxide dismutase (SOD) inhibitor. Aim of the present study was to investigate the histologic changes in pancreas after chronic administration of DDC.

Materials and Methods. Twelve Male Wistar rats were divided into two groups: 6 DDC rats and 6 control rats. The former were treated with IP injections of DDC at a dose of 500mg/kg body weight twice weekly and killed at 4 weeks. The latter were treated with IP injections of saline and killed at 4 weeks.

Results. Histological study of the pancreas revealed mild intra-, peri-, and interlobular fibrosis with mild acinar cell destruction at 4 weeks only in DDC rats.

Conclusion. Chronic IP injections of DDC, a known SOD inhibitor induced pancreatic fibrosis in rats.

THE EFFECT OF LEXIPAFANT ON NEUTROPHIL FUNCTION IN SEVERE ACUTE PANCREATITIS.

C. J. McKay, M. T. Sinclair, C. W. Imrie.
Department of Upper GI and Pancreatico-Biliary Surgery,
Royal Infirmary, Glasgow, UK.

Aims: Our group has shown that primed circulating neutrophils account for an increase in hydrogen peroxide production in patients with severe acute pancreatitis compared with healthy controls. We postulated that the reduction in organ failure scores seen in two human trials of Lexipafant in acute pancreatitis was due to the effect of this potent platelet activating factor (PAF) antagonist on neutrophil function.

Methods: 31 patients with severe acute pancreatitis (median APACHE II=10.5, IQR 9-12) were randomized to receive intravenous Lexipafant or placebo as part of a multicentre study. We measured circulating neutrophil priming and hydrogen peroxide production on admission and at 72 hours following the start of the infusion in 17 of these patients. Hydrogen peroxide production and priming of circulating neutrophils was measured using a previously described flow cytometric method. Mann Whitney U test was used for statistical analysis.

	Median Change in Neutrophil Priming (95% confidence interval)	Median Change in H ₂ O ₂ production (95% confidence interval)
Lexipafant	-23 (-57, 1.3)	-1.7 (3.7, -0.11)
Placebo	-19 (-40, 3.9)	-57 (-211, 93)
p value	0.7	0.4

Conclusion: Lexipafant does not significantly affect circulating neutrophil priming or hydrogen peroxide production in patients with severe acute pancreatitis.

CLINICAL SIGNIFICANCE OF MAGNETIC RESONANCE CHOLANGIOPANCREATOGRAPHY (MRCP) FOR CYSTIC TUMOR OF THE PANCREAS COMPARED TO ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY (ERCP)

K. Mera¹, H. Tajiri, M. Muto, A. Ohtsu, J. Furuse, K. Inoue², M. Konishi, T. Kinoshita, M. Ryu, S. Nawano³, K. Murakami, N. Moriyama, T. Hasebe³, K. Mukai, S. Yoshida⁴.
Depts. of Gastroenterology¹, Surgery², Radiology³, and Pathology⁴, National Cancer Center Hospital East, Kashiwa, Chiba, Japan.

Introduction. Cystic tumor of the pancreas has been investigated by a variety of imaging techniques. Though endoscopic retrograde cholangiopancreatography (ERCP) is well-known as one of the useful modalities, it is often difficult to diagnose the correct existence of the cyst or its characteristics due to a lot of mucin and/or a lack of the communication between the cyst and the main pancreatic duct in cystic tumor of the pancreas. Magnetic resonance cholangiopancreatography (MRCP) is being widely performed as a non-invasive diagnostic modality for investigation of the biliary tree and pancreatic duct system. In the present study, we compared MRCP images to ERCP, CT images and histological findings in order to clarify the diagnostic efficacy of MRCP for cystic tumor of the pancreas.

Patients and Methods. Fifteen patients with cystic tumor of the pancreas, surgically resected and histologically confirmed, were studied. They consisted of 5 cases of intraductal papillary adenocarcinoma, 5 of intraductal papillary adenoma, 2 of serous cystadenoma, 2 of retention cyst associated with invasive ductal carcinoma, and 1 of solid cystic tumor. All of them were examined by MRCP, ERCP and CT preoperatively at National Cancer Center Hospital East during the period from February 1995 to January 1998. MRCP images were compared to ERCP, CT images, and histological findings.

Results. MRCP images correctly identified the main pancreatic duct, the whole region of cystic tumor, and the communication between the cyst and the main pancreatic duct in all cases. On the other hand, ERCP demonstrated the cystic tumor and the communication between the cyst and the main pancreatic duct in only 9 of 15 cases (60%). Though sensitivity of CT images to recognize the septum inside the tumor was 93% and the solid component 88%, sensitivity of MRCP images for each appearance was 53% and 22%, respectively.

Conclusion. MRCP is capable of providing diagnostic information superior to ERCP for the diagnosis of cystic tumor of the pancreas. Though MRCP may provide complementary information about the whole region of interest, the characteristic features inside cystic tumor of the pancreas should be carefully diagnosed in combination with CT and endoscopic ultrasonography.

SPONTANEOUS APOPTOSIS AND PROLIFERATION IN HUMAN PANCREATIC CANCER

T Meggiato, *F Calabrese, E Favaretto, *E Ballelio, *M Valente, G Del Favero-Dept of Gastroenterology and * Dept of Pathology—University of Padova-ITALY

Introduction. The programmed cell death (PCD) is an active cellular process involved in cell deletion. Recently, several studies have documented the role of PCD in the development and/or progression of cancer. The aims of the study were to analyse 1. The spontaneous apoptosis in human pancreatic cancer; 2. Its association with the proliferation rate of the tumour; 3. The correlation of apoptotic index and mitotic index with the histological features of the tumour and the outcome of patients. **Patients and Methods.** 13 surgical specimens of ductal adenocarcinoma of pancreas were collected from patients who underwent potentially curative resection. No preoperative radio- or chemotherapy was performed. In these specimens we determine the apoptotic cell death by deoxynucleotidyl transferase (TdT) - mediated dUTP-degoxigenin nick end labelling (TUNEL). The proliferative activity was determined by immunohistochemistry using monoclonal antibody MIB-1. Apoptotic Index (AI) evaluated as a percentage of TUNEL-positive cells of 1,000 neoplastic cells and Mitotic Index (MI) evaluated as a percentage of positively stained nuclei /1,000 nuclei counted) were calculated in each case. Statistical analysis was performed by means of Pearson's and Fisher's exact test. TUNEL and Ki67 were expressed in neoplastic cells but not in normal tissue of the same specimen. **Results.** The AI was 49.0±47.9 and MI 12.8±10.2 (mean±S.D.) AI was higher in small (<4 cm) than in large (>4cm) tumours (80.3±56.1 and 20.7±13.1 respectively)(p<0.02). Cytological and architectural grading showed a positive correlation with AI (p<0.05 and p<0.05 respectively). No correlation was found between AI and stage, lymph node, vascular and perineural invasion (p ns). No correlation was found between AI and MI (p ns). Significantly higher values of AI were found in patients with short (5.17±4.3 months) as compared to long survival (26.1±23.3 months) (p<0.02). On the contrary patients with low MI values survived more than those with higher levels (6.83±4.1 and 25.1±20.1 months, respectively)(p<0.05). MI was correlated only with the stage of disease (p<0.03). **Conclusion** Our data suggest that 1. in pancreatic cancer the spontaneous PCD is more present in small tumours, with very low differentiation 2. patients with higher AI have a poor prognosis; 3. pancreatic cancer seems to differ from other tumours since PCD is not associated with cell proliferation and is an independent prognostic factor.

ENDOSCOPIC SURGERY OF CHOLEDOCHOCELES IN THREE CASES. TECHNIQUE, RESULTS AND REVIEW OF THE LITERATURE.

Miederer, S.E., Deyhle, P.
Bielefeld, Dept. Intern. Med., Johannes Hospital, Germany.

In three patients, 21, 44 and 67 years old, increasing abdominal pain had been present for 3, 11 and 17 years respectively. The symptoms were not related to either food intake or defecation. Laboratory findings revealed a mild cholestasis and hyperamylasaemia. In all cases the rare diagnosis of a choledochocoele (22 documented cases to date) could be established by hypotonic duodenography, ERCP and biopsy.

In 1974 we performed at the first time an endoscopically controlled electrocoagulatory ablation of the choledochocoele (case 1) under general anaesthesia using a snare. Three and four years later in case 2 and 3 resp. the procedure was simplified. An electrocoagulatory splitting was performed by means of a papillotomy without general anaesthesia. Prior to the operation, the

celes were maximally dilated (fig.) by injecting contrast medium through the natural openings. Then, in case 2, the papillotomy was also inserted through this opening (fig.). In case 3, the natural opening was located at the left lateral wall of the cele. Therefore, the papillotomy was inserted through a small medial incision. The length of the cut was related to the extension of the cele and reached 3 and 5 cm, respectively. The operations were performed without complications within 10 minutes. The abdominal pain ceased directly afterwards.

Annual controls following endoscopic splitting showed an unhindered outflow of contrast medium from the bile and pancreatic duct systems. Laboratory findings were within the normal range. There was no recurrence of the complaints. In case 1 however, a cholecystectomy was necessary because of cholecystitis four years after ablation. In the other cases cholecystectomy was performed before endoscopic splitting.

THE EFFECT OF CHRONIC EXERCISE ON PANCREATIC ACINAR CELLS IN RATS

K.Minato*, Y.Shiroya, Y.Nakae, T.Kondo.

Exercise Nutrition, Wayo Women's University, Chiba, Japan.

Introduction. Recently, we have found that chronic physical exercise such as endurance running training increases basal pancreatic protein content and basal amylase secretion. The purpose of the present study was to investigate the effect of the chronic exercise on pancreatic acinar cells in rats.

Methods. Female F344 rats (age, 6 weeks) were divided into a control (C; n=7) and an exercise (E; n=6) group. Food consumption was matched between the two groups. Rats in the C group were kept sedentary. Rats in the E group were exercised for 60 min a day (treadmill running final speed, 32 m · min⁻¹), 5 days a week during the experiment. After 8 weeks, the pancreas and hindlimb muscles were rapidly excised and weighed. Protein and DNA contents and enzymes activities in pancreatic tissue were measured. Pancreatic tissues were prepared for transmission electron microscopy.

Results. Inhibition of growth and hypertrophy of hindlimb muscles were recognized in the E group. Pancreatic wet weight, protein content, and amylase and lipase activities in the E group were significantly higher than in the C group. There was no significant difference in total DNA content in pancreas between the two groups. Electron micrographs revealed that acinar cells obviously hypertrophied and zymogen granules increased in the rats of E group compared with C group.

Conclusion. These results suggested that the chronic exercise causes the increase in pancreatic weight with hypertrophy of acinar cells. The increase of pancreatic protein content could be due to the increased synthesis and storage of exocrine enzymes.

DUODENUM-PRESERVING TOTAL PANCREATIC HEAD RESECTION FOR CYSTIC TUMOR OF THE PANCREAS - A NEW TECHNIQUES OF THE PRESEVATION OF THE VESSELS AROUND THE DUODENUM AND THE BILE DUCT.

S. Miyakawa, A. Horiguchi, K. Miura.

The 2nd Dept. of Gastroenterol. Surgery, Fujita Health University, Toyoake, Japan.

Introduction. The Beger's procedure is an organ-saving procedure in the treatment of severe chronic pancreatitis. However, there are some problems, when this procedure is indicated to the patients with low grade malignant cystic tumor. The paraduodenal pancreatic remnant may cause tumor remain and pancreatic fistula. Therefore, a duodenum-preserving procedure for low grade malignant cystic tumors is essentially a total resection of the head of the pancreas with the preservation of the blood supply to the bile duct and duodenum. We report a new techniques of the preservation of the vessels around the duodenum and the bile duct during total resection of the head of the pancreas.

Patients and Methods. This surgical procedure was performed in 3 patients with mucinous cystic tumors of the pancreatic duct in the head of the pancreas. The methods of the preservation of the vessels during the total resection of the head of the pancreas is to preserve the supra- and/or infra-pancreatoduodenal vein during the exploration of the mesenteric portal vein, to remain the duodenal branches of the anterior arterial arcade, one by one dividing the pancreatic branches, and not to dissect the pancreatic posterior membrane which the posterior arterial arcade runs under.

Results. The Operative time was 429 minutes, and the mean blood loss was 810 ml. The mean postoperative hospitalization was 20 days. None of the patients had early or late postoperative complications.

Conclusion. The new operative procedure, which preserves the vessels around the duodenum and the bile duct during total pancreatic head resection, freed us from early postoperative complications.

FAT ABSORPTION FOLLOWING VARIOUS RECONSTRUCTIONS OF PYLORUS-PRESERVING PANCREATO-DUODENECTOMY

S. Miyakawa, A. Horiguchi, K. Miura.

The 2nd Dept of Gastroenterol. Surgery, Fujita Health University, Toyoake, Japan.

Introduction. The superiority of various methods of reconstruction following pylorus-preserving pancreatoduodenectomy (PPPD) is unproven. We believe that the superiority should be demonstrated for patients with similar pancreatic exocrine function. Therefore we studied fat absorption after these operation using ¹³C-trioctanoin breath test. These operations were compared with respect to trioctanoin absorption for groups of patients classified by their pancreatic fibrosis.

Patients and Methods. We used two methods of reconstructions following the PPPD as follows: PG group (30 cases), Pancreato-gastrostomy, duodeno-jejunostomy and choledcho-jejunostomy were done in order; PJ-2 group (22 cases), Pancreato-jejunostomy, choledcho-jejunostomy and duodeno-jejunostomy in order. The breath test were performed on the patients who could tolerate a normal solid diet 1 to 3 months after operation. The patients in the groups were classified by the fibrosis of the pancreatic remnant, which was presumed the area of by measuring fibrosis of the transectional wedge of the resected pancreas histologically. We classified the fibrosis into three grades according to the degree of the fibrosis as follows: grade 0, < 10% fibrosis, grade 1, 10% to 30%; grade 2, > 30%.

Results. There were no significant differences in the ¹³C excretion rates and the cumulative values between the groups. The ¹³C excretion rates and the cumulative values in the patients with more than 30 % pancreatic fibrosis were lower than those in the patients with less than 30 % pancreatic fibrosis, regardless of the methods of reconstruction. The cumulative value in the PG grade 1 subgroup was significantly better than that for the PJ-2 grade 1 subgroup.

Conclusion. The results suggested that the ability of fat absorption following the PPPD is prescribed by the fibrotic area of the pancreatic remnant, and the methods of reconstruction of the PPPD

ACTIVATION OF IL-6 RECEPTOR AND RESISTANCE TO APOPTOSIS IN PANCREATIC CANCER CELLS

Y. Miyamoto*, R. Hosotani, M. Wada, J.-U. Lee, T. Koshida, K. Fujimoto, R. Doi, S. Tsuji, S. Nakajima, M. Imamura. Department of Surgery and Surgical Basic Science, Kyoto University, Kyoto, Japan.

Introduction. Various activities of Interleukin-6 (IL-6) are the result of its interaction with a membrane receptor consisting of an 80 kDa ligand-binding α subunit (gp-80), which triggers the association with a 130 kDa β subunit (gp-130), a common signaling component shared with other members of the IL-6 superfamily. Recent clinical publications have shown high serum levels of IL-6 in patients with surgical intervention or cancer-induced cachexia; however, functional analysis of IL-6 and its receptor has not been fully elucidated in the level of cancer cells. In this study, we examined the relationship between the expression and activation of gp-130 and the resistance to radiation-induced apoptosis in pancreatic cancer cell lines, and tried to clarify the molecular mechanism. **Materials and Methods.** Four human pancreatic cancer cell lines (CFPAC-1, HPAC, AsPC-1 and MiaPaCa-2) were employed. Levels of IL-6 in conditioned media were measured by ELISA assay, and phosphorylated gp-130 were detected by immunoprecipitation method (IP: anti gp-130 pAb, IB: anti p-Tyr mAb). Cells with phosphorylated gp-130 (CFPAC-1) and without phosphorylated gp-130 (AsPC-1) were treated with or without 50 ng/ml IL-6 and three experiments were done. 1) The effect to cell proliferation. 2) At the time points of 8, 12, 24, 48h, proteins were extracted and subjected to immunoblot analysis for Bcl-2 family proteins (Bcl-2, Bax and Bcl-X). 3) The cells were exposed to radiation ranging from 0 to 10 Gy and the number of attached cells was counted 48h later. **Results.** Levels of IL-6 in the media were as follows: CFPAC-1: 1900 pg/ml, HPAC: 51 pg/ml, AsPC-1: < 0.2 pg/ml, MiaPaCa-2: < 0.2 pg/ml. Phosphorylated gp-130 was detected in CFPAC-1 and HPAC, but not in AsPC-1 and MiaPaCa-2. IL-6 did not affect the cell proliferation in CFPAC-1 and AsPC-1. Expression for Bcl-2 and Bcl-XL protein were increased by IL-6 treatment in CFPAC-1 cells, but not in AsPC-1 cells.

Table. Cell survival ratio after irradiation (% control)

	5 Gy		10 Gy	
	IL-6(-)	IL-6(+)	IL-6(-)	IL-6(+)
AsPC-1 (gp-130 inactivated)	30 %	36 %	3 %	4 %
CFPAC-1 (gp-130 activated)	57 %	75 %	38 %	54 %

Conclusions. The results indicated that levels of IL-6 in the media and activation of gp-130 were correlated, and suggest that autocrine loop of IL-6 production might exist in pancreatic cancer cells. Exogenous IL-6 did not affect cell proliferation but significantly inhibited radiation-induced apoptosis. Up-regulation of anti-apoptotic Bcl-2 family proteins might be involved in this escape phenomenon.

A SOLID CYSTIC TUMOR OF THE PANCREAS IN A 12-YEAR-OLD BOY: TEN YEARS OF RECURRENCE-FREE FOLLOW-UP

S. Mizuno, M. Suzuki, F. Ito, K. Umeda

Department of Surgery, Kinan Hospital

Solid cystic tumor of the pancreas is rarely seen in young male. We report here a solid cystic tumor of the pancreas in a boy who had no recurrence for ten years. A 12-year-old Japanese boy was admitted to our hospital in September 1987 because of dull upper abdominal pain. On admission, a 6 cm tender, elastic hard, barely movable mass was palpable in the upper abdomen. Routine blood studies yielded values within the normal range, except for moderate elevation of T-bil (2.4 mg/dl), GOT (77 IU/L), GPT (105 IU/L), and ALP (84.9 KA). Serum neuron-specific enolase (NSE) was elevated to 24 ng/ml (normal range: <10). The serum levels of gastrointestinal hormones such as insulin, glucagon, somatostatin, and gastrin were all within normal limits. US and a CT scan revealed an encapsulated, cystic mass with a solid component, 6 cm in diameter, located in the head of the pancreas, and a dilated gallbladder and intrahepatic bile duct. PTGBD was performed and cholangiography demonstrated obstruction of the common bile duct. Celiac angiography revealed a hypovascular mass. A solid cystic tumor was suspected, and pylorus-preserving pancreaticoduodenectomy was performed. The resected tumor measured 7.0 × 6.5 × 6.0 cm, and was covered with a firm, fibrous capsule. Histological examination revealed that the cyst was lined by pseudopapillary epithelial cells, and mitoses were rare. Immunohistochemical studies showed immunoreactivity for a α 1-antitrypsin alone, with no cells being reactive for carcinoembryonic antigen, insulin, glucagon, somatostatin, or gastrin. We determined the tumor to be a solid cystic tumor of the pancreas. The patient has been well for ten years since surgery, with no signs of recurrence.

A MURINE MODEL FOR HUMAN PANCREATIC CANCER -- ORTHOTOPIC INJECTION OF SYNGENEIC PANCREATIC TUMOR CELLS

K. Morikane*, R. Tempero, M. Hollingsworth.

Eppley Institute, University of Nebraska Medical Center, Omaha, Nebraska, USA.

We are studying the influence of site of tumor growth, route of immunization, and immunological tolerance on the induction of immunity to MUC1, a human glycoprotein.

C57BL/6 mice (w/t) and C57BL/6 transgenic for MUC1 (MUC1-Tg) were challenged with Panc02-MUC1, a syngeneic pancreatic cancer cell line expressing human MUC1, either orthotopically (into the pancreas) or subcutaneously. All w/t mice rejected tumor cells injected subcutaneously at a dose of 1×10^5 cells but 7 out of 10 (70%) did not reject tumors injected orthotopically. MUC1-Tg mice did not reject tumor cells injected by either route. Sera from w/t mice that rejected Panc02-MUC1 at the orthotopic site showed no detectable IgG1 and IgM against MUC1 tandem repeat. Mice in which Panc02-MUC1 grew progressively showed significant IgG1 and IgM titers, suggesting that a humoral immune response to the MUC1 tandem repeat was ineffective for rejection of Panc02-MUC1 and that tumor rejection was cell-mediated. w/t mice were protected against orthotopic challenge with Panc02-MUC1 by two different procedures: (1) Preimmunization of w/t mice with a low dose of Panc02-MUC1 subcutaneously; or (2) Adoptive transfer of spleen and lymph node cells harvested from mice immunized with Panc02-MUC1 subcutaneously. This demonstrates that immune responses against MUC1 can be detected and adoptively transferred.

These results suggest that the orthotopic site is more favorable for growth of Panc02-MUC1 than the subcutaneous site and that it is more difficult to produce immune responses to tumors growing at this site. Nonetheless, Panc02-MUC1 cells growing in the pancreas are accessible to the immune system. We are currently evaluating different immunization protocols and the immune cell types involved in this protective response.

GASTROBILIARY MOTILITY IN CHRONIC PANCREATITIS PATIENTS WITH AND WITHOUT ENZYME SUBSTITUTION

T. Mizushima, K. Ochi, N. Matsumura, H. Harada. Department of Laboratory Medicine, Okayama University Medical School, OKAYAMA, JAPAN

Introduction. Our previous study suggested that the rapid gastric emptying and impaired gallbladder contraction in patients with chronic pancreatitis (CP) was due to depleted pancreatic lipase output. We tested whether oral pancreatic enzymes can improve the results.

Patients and Methods. Study subjects comprised 17 healthy controls and 20 patients with CP. We studied gastric emptying time (GET) and gallbladder contraction (GBC) in response to a mixed liquid meal. Thirteen patients had an initial study using a test meal without pancreatic enzymes, followed on separate days by a test meal with pancreatic enzymes (Excelase®, Meiji-Seika Corp., Tokyo). Blood samples were taken before and 2 hours after the test meal to determine the pancreatic polypeptide (PP) levels.

Results. In patients with CP, GET was faster (92.9 ± 26.6 min vs. 129.7 ± 26.0 min), GBC at 15 min after meal was impaired ($45.7 \pm 17.0\%$ vs. $58.1 \pm 16.0\%$), and the ratio of pre- to post-prandial PP levels was enhanced (1.93 ± 0.6 vs. 1.28 ± 0.35). Oral administration of a capsule of Excelase significantly improved GET (107.6 ± 19.7 min), GBC rate at 15 min ($51.2 \pm 20.3\%$), and the PP ratio (1.73 ± 1.25).

Conclusion. Oral pancreatic enzymes improved gastro-biliary dysmotility, confirming the previous findings that suggested the depleted pancreatic enzyme output as a cause of the dysmotility. Gastrointestinal hormones such as PP are likely to mediate the pathophysiology.

CURATIVE RESECTION OF ORTHOTOPICALLY IMPLANTED PANCREATIC CANCER IN SYRIAN GOLDEN HAMSTERS - IS IT POSSIBLE? -

C.Y. Morioka*, S. Saito, K. Kita, K. Ohzawa, A. Watanabe

Third Department of Internal Medicine, Toyama Medical and Pharmaceutical University, Toyama, Japan

Introduction: Orthotopic pancreatic cancer implantation models in heterologous or homologous animals have been reported recently. It is not clear whether early pancreatic resection can bring complete cure in such tumor-bearing animals. The purpose of this study was to clarify the possibility of curative resection in orthotopically implanted hamster experimental pancreatic cancer model.

Materials and Methods: HaP-T1, a BHP-induced, moderately differentiated hamster pancreatic cancer cell line, established in our laboratory, was implanted into the splenic lobe of the pancreas of twenty syngeneic Syrian golden hamsters. They were divided in two groups: orthotopic cell implantation and orthotopic tissue implantation. Partial pancreatectomy was performed in the 1, 2, 3, and 4th weeks after implantation. The resected specimens were examined histologically whether their margin were free of tumor infiltration. The general state and weekly-body weight of the animals were followed up as far as they survived. The animals were necropsied immediately after death. Four hundred days after the tumor resection, the surviving hamsters were sacrificed and also investigated whether they had histological and/or genetic metastases, by detecting *K-ras* point mutation using PCR-RFLP method.

Results: All the surgical specimens were confirmed as having pancreatic neoplasm. Tumor implanted hamsters without pancreatectomy died before 75 days. The animals in which pancreatectomy was performed later than 15 days after implantation, died before 120 days due to local recurrence and/or metastases. Five hamsters survived until 400 days after tumor removal: two of cell implantation group, which underwent resective surgery at 7th and 13th day, and three of tissue implantation group, operated after 10, 14 and 15 days after the implantation. Furthermore, none of the survived hamsters had histological nor genetic metastases.

Conclusions: The present study clearly showed that the early pancreatic resection, i.e., before 15 days with free margins, could bring complete cure in the orthotopically implanted pancreatic cancer model of Syrian golden hamsters. This model would be useful for further research of adjuvant or neoadjuvant therapy in pancreatic carcinoma.

POST OPERATIVE COMPLICATIONS OF WHIPPLE OPERATION WITH RECONSTRUCTION IN SINGLE LOOP AND DUCT-TO-MUCOSA ANASTOMOSIS

C.Y. Morioka ^{*1,2,3}, F. Callejas Neto³, S. Saito¹, M. Shimoda², J.C. Pareja³, V.F. Pilla³, T. Sakamoto², A. Watanabe¹, K. Tsukada², L.S. Leonardi³
 Third Depart. of Internal Medicine¹, Second Depart. of Surgery², Toyama Medical and Pharmaceutical University, Japan, and Depart. of Surgery, School of Medical Sciences, Campinas State University, Brazil ³

Introduction: Pancreas cancer is the fifth cause of cancer death in Brazil. Whipple operation is the most common surgical procedure performed as a challenge of cure. However, it has different operative mortality rates depending on the center, surgeon experience, post operative cares and so on. Specialized centers seem to have low morbidity. This time, we would like to show our institution data and experience.

Patients and Methods: Thirty three patients who underwent duodenopancreatectomy with reconstruction in single loop and duct-to-mucosa anastomosis (between pancreatic duct and jejunal loop) were analyzed retrospectively. The surgeries were done between 1991 and 1994, in Campinas State University Hospital, Brazil. Nineteen of the patients were male (57.5%) and 14 were female (42.5%), with median age of 61 years (range: 30 to 75 y.o.). Pathologic examination results showed: adenocarcinoma of duodenal papilla in 19 patients (57.5%), pancreatic head cancer in 11 patients (33%), adenocarcinoma of bile duct in two (6%) and non-functioning endocrine tumor in one case. The reconstruction technique performed in all cases was jejunal single loop (Whipple modified): 1. hepaticojejunostomy with interrupted sutures, 2. pancreatic duct and jejunal loop in two layers using Maxon 5.0®: 1st- Wirsung duct and jejunal mucosa anastomosis in interrupted sutures, 2nd- interrupted sutures between jejunal seromuscular layer and the pancreas, 3. gastrojejunostomy in interrupted sutures. It was left Multifisternated Levine® catheter through pancreatic duct-mucosal anastomosis.

Results: As immediate post operative complications, we observed: 1 case of pneumonia, 1 case of pleural effusion, 1 case of digestive bleeding from gastric jejunal anastomosis, 2 cases of wound infection, 2 cases of prolonged ileus, 2 cases of biliary fistula. There were no cases of pancreatic fistulas. There were no deaths during the hospitalization time (median: 10 days).

Conclusions: Our study suggests that duodenopancreatectomy is a procedure able to be performed with low rates of post-operative complications in tertiary hospitals.

GENE EXPRESSION OF PANCREATITIS-ASSOCIATED PROTEIN IN RAT SPONTANEOUS CHRONIC PANCREATITIS

Y. Motoo, S.-B. Su, H. Taga, M.-J. Xie, J. Sakai, N. Sawabu
 Department of Internal Medicine, Cancer Research Institute, Kanazawa University, Kanazawa, Japan

Introduction. Pancreatitis-associated protein (PAP) is almost absent in normal pancreas, but is overexpressed in acute pancreatitis. However, the pathophysiological significance of PAP in chronic pancreatitis is unknown. The aim of this study is to analyze the gene expression of PAP in a rat spontaneous chronic pancreatitis model.

Materials and Methods. Four-week old male WBN/Kob rats were fed with a special pellet diet (MB-3) for 20 weeks. The rats were sacrificed at 4-week intervals, and the pancreata were removed. The pancreatic tissues were histopathologically examined. PAP mRNA was detected by an RT-PCR method. Semiquantitative analysis on the RT-PCR results was performed using a computer scanning of PAP and beta-actin (internal control) mRNA bands on an agarose gel electrophoresis. The cellular localization of PAP mRNA was analyzed by *in situ* hybridization (ISH) using biotin-labeled PAP cDNA probe (777 bp). Chaihu-guizhu-tang (TJ-10) was orally administered as drug therapy. Camostat mesilate (Foiapan) was used as a control drug.

Results. Pathological changes of chronic pancreatitis were first seen in 12-week-old WBN/Kob rats. Inflammation and fibrosis progressed thereafter, and at the age of 24 weeks, dense fibrosis almost replaced the normal acinar structure. Interestingly, PAP mRNA was detected at 8 weeks when the pancreatic histology was still normal. The expression of PAP mRNA was highest at 12 weeks and gradually decreased. PAP mRNA was expressed in the cytoplasm of acinar cells in the analysis of ISH. ISH confirmed the RT-PCR results showing the PAP mRNA expression in acinar cells in 8 and 12 weeks. TJ-10 inhibited the development of chronic pancreatitis at 12 and 16 weeks almost completely, and the pathological changes at 20 and 24 weeks in the TJ-10 group were milder than those in the non-treated group. PAP mRNA was not expressed in the TJ-10 group at 8, 12, and 16 weeks, but it was weakly expressed at 20 and 24 weeks. The effect of TJ-10 was comparable to that of camostat mesilate.

Conclusions. PAP mRNA was expressed before the pathological onset of chronic pancreatitis and the peak expression of PAP mRNA coincided with the onset of chronic pancreatitis. PAP mRNA expression was markedly decreased with drug therapy.

PANCREATITIS IN LATE CHILDHOOD AND ADOLESCENCE

Y. Morita, S. Okamoto, N. Hirahara, T. Moriai, * I. Makino.

Second Department of Internal Medicine, Megumino Hospital, Eniwa, Japan. * Second Department of Internal Medicine, Asahikawa Medical College, Asahikawa, Japan.

Acute pancreatitis unusual in late childhood and adolescence, and chronic pancreatitis is even less common. We have reported three cases of acute pancreatitis and two cases of chronic pancreatitis with history of onset at less than twenty years old.

Case1: 17-year-old boy had acute pancreatitis. CT Grading was D.

Case2: 9-year-old girl had with traffic injury and had occurred acute pancreatitis after two months of the neurosurgery. CT Grading was E.

Case3: 17-year-old boy had repeated mild acute pancreatitis from eleven years old. CT Grading was B. He was treated with steroid therapy for the paralysis of right optic nerve on nine years old.

Case4: 11-year-old boy had surgical operation for the stenosis of duodenum on his birth. He had frequently abdominal pain from three years old. We have diagnosed him chronic pancreatitis with pancreatolith and found the lack of pancreatic tail.

Case5: 20-year-old man had mild acute pancreatitis. CT Grading was B. We had detected tumor of pancreatic tail. As a result of distal pancreatectomy, tumor was chronic localized pancreatitis of the pancreatic tail.

The most frequent cause of acute pancreatitis at juvenile onset is anomalous arrangement of the pancreaticobiliary ductal system in Japan. Endoscopic retrograde cholangiopancreatography (ERCP) was performed in all patients and no patients have this anomaly.

Hyperlipidemia, hypercalcemia and virus infection were not detected in all patients. No patients had a family history of pancreatitis. Injury and surgery in Case 2, drug (steroid) in Case 3 and abnormality of pancreas and surgery in Case 4 might cause the pancreatitis.

However a definitive etiological relationship is difficult to prove.

TELOMERASE ACTIVITY IN PURE PANCREATIC JUICE FOR THE DIAGNOSIS OF PANCREATIC CANCER MAY BE COMPLEMENTARY TO K-RAS MUTATION

S.J. Myung*, Y.S. Kim, D.W. Seo, K.N. Shim, S.H. Yang, E.R. Park, S.K. Lee, M.H. Kim, Y.I. Min
 Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Introduction: To develop diagnostic assays that can identify patients with pancreatic cancer early in the course of disease, the use of molecular techniques is a promising new area of investigation. K-ras mutation in pancreatic juice has been shown to be positive in up to 70% of pancreatic cancer. However, the usefulness of K-ras mutation in the diagnosis of pancreatic cancer is questionable due to its high false positive and false negative values. Telomerase is a ribonucleoprotein enzyme necessary for the synthesis of telomeres. In contrast to normal somatic cells, cancer cells are characterized by the aberrant expression of telomerase. We conducted this study to determine the usefulness of the K-ras mutation and telomerase activity in pancreatic juice for the diagnosis of pancreatic cancer.

Patients and Methods: The pure pancreatic juice was examined in 31 patients: 12 with ductal cell carcinoma of the pancreas, 11 with chronic pancreatitis, and 8 controls. About 15-20 ml of pancreatic juice was collected during ERCP after secretin stimulation. The K-ras gene was amplified by enriched PCR and the mutation at the codon 12 was examined by direct sequencing. Telomerase activity was detected by telomeric repeat amplification protocol (TRAP, Oncor).

Results:	K-ras mutation	Telomerase	Both
Pancreatic cancer (n=12)	9	11	8
Chronic pancreatitis (n=11)	3	2	0
Controls (n=8)	0	0	0
Sensitivity	75%	92%	67%
Specificity	84%	89%	100%

Conclusions: For the diagnosis of pancreatic cancer, telomerase activity in pancreatic juice may serve as a possible useful tool complementary to the K-ras mutation because it may decrease the false positive rates.

RETROPANCREATIC INVASION OF CARCINOMA OF THE HEAD OF THE PANCREAS

T. Nagakawa, T. Ohno*, M. Kayahara*, H. Kitagawa*, K. Ueno*, I. Komishi*
Department of Health and Science (IInd Surgery), School of Medicine, Kanazawa University, Kanazawa, Japan.

Introduction. We evaluated the correlation between retropancreatic invasion and other spreading factors, and clarified histologically the pattern of retropancreatic invasion in carcinoma of the head of the pancreas based on resected specimens.

Subjects and Methods. Since 1973, 159 patients with cancer of the head of the pancreas have undergone surgical exploration. Resection was performed in 80 patients (50.3%), including 64 patients (40.3%) undergoing curative resection based on macroscopic criteria, and 44 patients (27.7%) undergoing curative resection based on microscopic criteria. Tumor infiltration of 64 patients undergoing macroscopically curative resection were evaluated. Continuously, we studied the direction of the retropancreatic invasion toward the superior mesenteric artery (SMA), the portal vein (PV) and the inferior vena cava (IVC) in selected 21 patients with retropancreatic invasion among the 64 patients.

Results. The overall 5-year survival rate was 21.0% in this macroscopically cured group and 30.6% in the microscopically cured group. Retropancreatic invasion (rp) was observed in 64 patients undergoing macroscopically curative resection. The number of patients with rp0 was 12, rp1 10, and rp2 26. Totally, twenty patients (31.3%) were positive invasion to the surgical margin (ev2). The 5-year survival in patients with rp0 (n=12) was 65.6%, rp1 (n=7) 21.4%, and rp2 (n=21) 19.0%. R(rp) correlated with invasion of the portal vein, invasion of the extrapancreatic nerve plexus and lymph node involvement, but not with tumor size. The mean distance of histologic spread, including lymphatic and perineural spread, toward the blood vessels was 3.2 mm (0 to 13.2mm) in the direction of SMA, 0.5 mm (0 to 2.0 mm) in the direction of PV, and 2.1 mm (0 to 4.8 mm) in the direction to IVC.

Conclusion. Those results demonstrated that complete resection of the nerve plexus is necessary for pancreatic cancer, and retropancreatic dissection with wide margins combined with resection of the portal vein is essential.

(a) TRYPSINOGEN GENE MUTATION IN JAPANESE PATIENTS WITH JUVENILE OR FAMILIAL PANCREATITIS.

(b) Y. Nagasaki, M. Koizumi, T. Shimosegawa, H. Takano, M. Uchi, A. Takayama, Y. Matsubara, K. Narisawa and T. Toyota.

(c) The Third Department of Internal Medicine and Department of Biochemical Genetics, Tohoku University School of Medicine, Sendai, Japan

Introduction. Hereditary pancreatitis (HP) is an autosomal dominant disorder, and not distinguished from pancreatitis due to other causes with the conventional morphologic or biochemical markers. Since a high risk of pancreatic cancer in HP has been reported, it is important to make precise diagnosis of HP for the prediction of prognosis. However, the diagnosis of HP in Japan by means of family tree study is difficult due to decreasing number of children in this country. Recently Whitcomb et al. reported that a point mutation in trypsinogen gene could cause HP. Their observation opened the way to gene diagnosis of HP. Thus far, two mutations have been described: a G-to-A transition in exon 3 (R117H) and an A-to-T (N21I) change in exon 2. The aim of this study is to assess the contribution of trypsinogen gene mutation on juvenile or familial pancreatitis in Japanese patients.

Patients and Method. Genomic DNA was extracted from 24 patients who showed symptoms of the pancreatitis in childhood and/or had affected family member(s) and four healthy relatives in 17 families. R117H mutation was examined by Afl III digestion of PCR-amplified DNA fragments and N21I mutation was inspected by direct sequencing.

Results. R117H mutation was found in four families. Families A, B and C had four affected patients respectively. In family D, two brothers were patients. N21I mutation was detected in no families. The R117H mutation is a common mutation among American and Italian patients.

Conclusion. It occurred at CpG mutation hot spot, which might explain the identification of the same mutation in genetically different Japanese population. It showed also that the gene mutation analysis could contribute to diagnosis of HP in the case having an insufficient family history.

Treatment of Severe Acute Pancreatitis by Continuous Regional Arterial Infusion of a Protease Inhibitor and Antibiotics

T. Naganuma, H. Sasaki, H. Kuroda, A. Ito, H. Kato, K. Fujimori, N. Terada and Y. Kawarada*

Dept. of Surgery and Radiology, Saiseikai Matsusaka General Hospital, 1st Dept. of Surgery, Mie University School of Medicine*

Introduction: We assessed the clinical efficacy and problems associated with continuous regional arterial infusion of a protease inhibitor and antibiotics (CAI) for severe acute pancreatitis.

Material & Methods: The subjects were the 3 patients in whom CAI was performed among the 6 patients with severe acute pancreatitis (AP) we encountered during the past 3 years. The etiology of the AP was alcohol in 2 cases and idiopathic in 1. The patients' age was 44-87 years, and all were males. As indications of the severity of the AP, the prognosis scores (PS) were 2-8.5, and the APACHE-II scores (AP-II) were 13-29. The CT grade was "grade IV" in all cases, and there was pancreatic necrosis in 2 cases and peripancreatic fat necrosis in 1 case. PS and CT grades were calculated according to the criteria of the Japan Intractable Pancreatic Diseases Study Group. A combination of Nafamostat mesilate 120 mg/d and imipenem 1 g/d was continuously infused. The tip of the catheter was positioned in the celiac artery, the common hepatic artery, and the splenic artery in one case each. CAI was started 24-48 h after the onset of pancreatitis, and was performed for 7-14 days. Other special interventions consisted of concomitant peritoneal lavage and CHDF in one case each.

Results: A rapid pain-relieving effect was observed in all three cases. Improvements in PS and AP-II were noted in all 3 patients. There was marked improvement in the CT grade in 1 patient and no change in 1 patient, and it has not been determined in the remaining patient. Organ injuries all improved. Splenic infarction was observed as a complication of CAI in 1 patient. The outcome was survival in 2 cases, in 1 of which severe pneumonia and ARDS developed as late complications, but the patient was saved by intratracheal injection of alveolar surfactant. The single death occurred in an 87-year-old patient with associated peripancreatic fat necrosis that extended beyond the pancreas, and the patient died of MOF.

Conclusion: 1. CAI was useful as a method of preventing and controlling pancreatic necrosis and MOF in acute pancreatitis. 2. Not only the CT finding, but PS and the AP-II, are useful in judging the efficacy of CAI. 3. Measures to prevent and control extensive progression of the inflammation beyond the pancreas will be a future task.

CONTRAST-ENHANCED ULTRASONOGRAPHY WITH CARBON DIOXIDE INJECTION FOR TUMORS OF THE PANCREATIC HEAD

S. Nakagawa¹⁾, T. Imai¹⁾, T. Higashiguchi¹⁾, K. Tanigawa¹⁾, Y. Kawarada²⁾

Dept. of Surgery, Suzuka General Hospital, Mie, Japan¹⁾, First Dept. of Surgery, Mie University School of Medicine, Mie, Japan²⁾

Introduction. We present our clinical experience with contrast-enhanced ultrasonography in the differential diagnosis between mass-forming chronic pancreatitis and pancreatic cancer.

Patients and Methods. Six patients (3 with chronic pancreatitis and 3 pancreatic cancer) were examined by carbon dioxide contrast-enhanced ultrasonography (CO₂-US), in which abdominal US was performed with CO₂ micro-bubble intra-arterial infusion during angiography, and by various other imaging methods such as CT scan, MRI, EUS, ERCP, and AAG.

Results. Conventional imaging methods failed to differentiate chronic pancreatitis from pancreatic cancer because of similar abnormal findings. However, CO₂-US showed clear iso-enhancement of the masses in the pancreatic head in the 3 cases of chronic pancreatitis. In the 3 cases of pancreatic cancer, on the other hand, CO₂-US showed hypo-enhancement of the tumors. The preoperative diagnosis was easy to make on the basis of the CO₂-US findings. The final diagnosis was made intraoperatively, and 3 bypass operations and 3 pancreatoduodenectomies were performed.

Conclusion. Differential diagnosis between mass-forming chronic pancreatitis and pancreatic cancer was accomplished preoperatively by using pancreatic CO₂-contrast enhanced ultrasonography.

THE EFFECT OF CCK ON PANCREATIC BLOOD FLOW IN CONSCIOUS DOGS

M. Nakajima*, S. Naruse, M. Kitagawa, H. Ishiguro, O. Ito, H. Ieda, Y. Seki, S. Ko, N. Mizuno, T. Yoshikawa, M. Mori, T. Hayakawa. Department of Internal Medicine II, Nagoya University School of Medicine, Nagoya, JAPAN.

Introduction. The mechanisms which mediate pancreatic blood flow are not well understood. In this study we have investigated the effect of CCK on pancreatic blood flow, systemic arterial pressure, and heart rate and compared them with those of stomach and intestine in 5 conscious beagle dogs.

Methods. Under ether anesthesia, flow probes of transit-time blood flow meters were placed around a pancreatic branch of the splenic (PA), left gastric (LGA) and superior mesenteric arteries (SMA). Chronic gastric and duodenal fistulae were constructed and a catheter of the blood-pressure sensor for a telemetry system was placed inside the femoral artery. After a recovery period of one month, blood flow of PA, LGA and SMA, systemic blood pressure, and heart rate were measured in the conscious state under a constant intravenous administration of CCK-8 (200ng/kg/hr), loxyglumide (10mg/kg/hr) or CCK-8 plus loxyglumide.

Results. The mean blood flow of PA during the fasting quiescent phase was 3.0 ± 0.7 ml/min. Pancreatic blood flow rapidly increased to 18.2 ± 3.4 ml/min after the intravenous administration of CCK-8, while blood flow of LGA and SMA, systemic blood pressure, and heart rate did not change. The intravenous infusion of loxyglumide did not affect the resting PA blood flow, but suppressed PA blood flow response to CCK-8.

Conclusion. In dogs, CCK-8 increases PA blood flow without affecting blood pressure and blood flow of LGA and SMA. Loxyglumide inhibits PA blood flow response to CCK-8, which suggests that pancreatic vasodilatation induced by CCK-8 is mediated by the CCK-A receptor.

POSTOPERATIVE LIVER FUNCTION PREDICTED BY PREOPERATIVE ^{99m}Tc-GSA LIVER SCINTIGRAPHY IN PATIENTS WITH PERIAMPULLARY CARCINOMAS COMPLICATING OBSTRUCTIVE JAUNDICE

H. Nakano (1), K. Kumada (1), Y. Takekuma (2), R. Fujita (2), M. Yamaguchi (1) Department of Surgery (1), and Gastroenterology (2), Showa University Fujigaoka Hospital, Yokohama, Japan.

Introduction. Technetium-99m galactosyl human serum albumin (Tc-GSA) is a novel liver scintigraphic agent. The aim of the present study was to examine whether liver scintigraphy with this agent performed before biliary drainage could predict outcome of biliary drainage in patients with periampullary carcinomas complicating obstructive jaundice. We also investigated whether this liver scintigraphy could predict postoperative liver function in these patients undergoing pancreaticoduodenectomy.

Patients and Methods. Tc-GSA liver scintigraphy was performed in 13 patients with periampullary carcinomas complicating obstructive jaundice. Each patient underwent standard pancreaticoduodenectomy after biliary drainage. Maximum removal rate of Tc-GSA (GSA-Rmax; standard normal value ≥ 0.60) was calculated using a radiopharmaceutical five-compartment method. Efficacy of preoperative biliary drainage was assessed with decrease of serum total bilirubin concentration for the initial 1 week after the biliary decompression. Postoperative liver function was assessed with increase of serum bilirubin concentration, which was calculated by the difference between bilirubin concentration immediately before surgery and maximum bilirubin concentration after the surgery.

Results. Decrease of serum bilirubin 1 week after biliary drainage were higher in the GSA-Rmax ≥ 0.60 group than in the GSA-Rmax < 0.60 group (8.1 ± 1.3 vs. 3.0 ± 1.3 mg/dl/week, $p < 0.05$). Postoperative bilirubin increase was significantly lower in the GSA-Rmax ≥ 0.60 group than in the GSA-Rmax < 0.60 group (0.7 ± 0.4 vs. 4.8 ± 1.3 mg/dl, $p < 0.05$). A multivariate analysis showed that GSA-Rmax measured before biliary drainage significantly predicted postoperative bilirubin increase ($p < 0.05$).

Conclusions. These results suggest that technetium-99m galactosyl human serum albumin liver scintigraphy is useful for predicting outcome of biliary drainage and postoperative hepatic dysfunction in patients with periampullary carcinomas complicating obstructive jaundice, who underwent pancreaticoduodenectomy.

DETECTION OF K-RAS GENE MUTATION IN PLASMA DNA OF PATIENTS WITH PANCREATIC CANCER

S. Nakamori*, T. Yamada, H. Ohzato, S. Oshima, T. Aoki, N. Higaki, H. Nagano, K. Dono, M. Sakon, M. Gotoh, M. Monden. Department of Surgery II, Osaka University Medical School, Suita, Osaka, Japan.

Introduction. K-ras gene mutations in codon 12 are frequently found in pancreatic ductal adenocarcinoma. Detection of these mutations have been focused for screening and diagnosis of the disease. The aim of this study is to examine the potential usefulness of the detection of K-ras gene mutations in plasma DNA from the patients with pancreatic ductal adenocarcinoma. **Patients and Method.** K-ras gene mutations in codon 12 were examined by mutant allele specific amplification method (MASA) in DNAs extracted from surgical specimen and plasma obtained from 21 patients with pancreatic adenocarcinoma and four with chronic pancreatitis.

Results. K-ras gene mutations in codon 12 were detected in DNA from 15 of 21 (71%) primary tumors. In nine of 15 (60%) patients with the K-ras gene mutation positive tumors, the identical K-ras gene mutations were detectable in their plasma DNA. Neither of the patients with chronic pancreatitis nor healthy volunteers demonstrated the mutated DNA in plasma. Tumors positive for the K-ras gene mutations in plasma DNA were more likely to be large ($p < 0.05$) and chance for palliative treatment ($p < 0.1$) than those negative for K-ras gene mutations in plasma DNA, while other clinicopathological features such as histologic type, mode of invasion and metastasis dose not correlate with K-ras gene mutation status in plasma DNA. K-ras gene mutations in plasma DNA were not detectable after treatments in six of nine (67%) patients.

Conclusion. K-ras gene mutations can be detectable in circulating DNA extracted from the plasmas of the patients with pancreatic ductal adenocarcinoma. The monitoring of the K-ras mutations in plasma may be clinically applicable to evaluate the development of tumor and efficacy of treatments for the disease.

GDA PRESERVING PANCREATIC HEAD RESECTION WITH SEGMENTAL DUODENECTOMY

A. Nakao*, T. Kaneko, T. Nonami, T. Kurokawa. Department of Surgery II, Nagoya University Hospital, Nagoya, Japan.

Introduction. Duodenum-preserving pancreatic head resection has been performed for benign pancreatic head diseases. Complete resection of the pancreatic head with preservation of common bile duct and duodenum sometimes causes common bile duct or duodenal necrosis due to ischemia. We propose a simple, easy and safe procedure for complete resection of pancreatic head with segmental duodenectomy and preservation of the gastroduodenal artery (GDA) to prevent complications which may be caused on duodenum preserving pancreatic head resection.

Operative Procedure. Pancreatic head resection with segmental duodenectomy including minor and major papilla was performed for mucin-producing tumor of the pancreatic head. By preservation of the right gastric artery, supraduodenal artery and GDA, 5 to 7 cm of the first portion of the duodenum is preserved with good arterial circulation. By preservation of the anterior inferior pancreaticoduodenal artery, the third portion and anal side of the second portion of the duodenum are preserved with good arterial circulation. Complete pancreatic head resection with 3 to 4 cm of segmental duodenectomy including minor and major papilla is completed. Tumor extension in the main pancreatic duct of the remnant pancreas was studied using ultra-thin pancreatoscope. Reconstruction of the alimentary tract is performed with pancreatogastrostomy, end to end duodenoduodenostomy and end to side choledochoduodenostomy.

Results. In 15 cases of pancreatic head diseases, chiefly benign tumors, this procedure was successfully performed without severe complications. Postoperative QOL was quite satisfactory.

Conclusion. Complete resection of pancreatic head for benign tumor of the pancreatic head region can be performed with safety and ease by this procedure.

STUDY OF THE COMBINATION THERAPY (EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY (ESWL) + ENDOSCOPIC THERAPY) FOR PANCREATOLITHIASIS

D.Nakayama, M.Furukawa, H.Matsubayashi, M.Yamada, S.Kokuno, T.Mizoue, Y.Mizumura, S.Ogiwara, S.Niki, K.Onoda, K.Miwa, Y.Magami, T.Honobe, T.Niido, T.Seki, T.Saitou

Dept. of 4th Internal Medicine, Tokyo Medical College

[Aim] The aim of our study was to evaluate the combined effect of ESWL and endoscopic therapy for pancreatolithiasis. **[Patients and Method]** We studied 19 cases with pancreatolithiasis including 14 cases of male and 5 cases of female and were divided to two groups, single therapy group (ESWL only) (Group A) and combined therapy group (Group B). The average age of the subjects was 50.7. The combined therapy applied to 10 cases in whom intraductal multiple pancreatic stones and stenosis of pancreatic ducts were treated with both ESWL and endoscopic therapy including endoscopic pancreatic sphincterectomy (EPST) (5 cases), stone disintegration therapy using balloon or basket catheter (5 cases), endoscopic naso pancreatic drainage (ENPD) (8 cases), and stenting of pancreatic duct (4 cases). The endoscopic therapy was performed in order to extract stones, drainage pancreatic juice and fragments of stones, and focus the shock wave under pancreaticography. **[Results]** Concerning about the age and maximum diameter of stone, there was no difference between Group A and B. The number of the cases who had various number of stones (1-24) in Group A and B were (1, 3, 5) and (1, 1, 8), respectively. The total number of the times of ESWL and the total number of the shock wave discharges in Group A and B were 5.4 and 10.2, 20656 and 39446, respectively. Regarding about exocrine function (PFD) and endocrine function (OGTT), there was no difference between Group A and B. The duration of hospital treatment in Group A and B were 48.1 and 79.5, respectively. The total number of the times of therapy, the total number of the shock wave, and the duration of the therapy in Group A were larger than in Group B, because the number of stone of the patients in Group A was also larger than that of Group B. **[Conclusion]** We concluded that combination management (ESWL with endoscopic therapy) could improve the effect of therapy even if patient has a lot of stones.

ECTOPIC ANTROPILORIC PANCREAS - A DIFFICULT DIAGNOSIS.

S.Neagu, S.Rohr, F.Faure, A.Derlon, N.de Manzini, M.P.Chenard, Ch.Meyer

CHU Haute-pierre, Strasbourg, France.

The retroperitoneal site of pancreas, his relatively small bulk and his intimate relation with the neighboring digestive and nondigestive structures confers an extreme difficulty to diagnosis of some masses with this topography. Sometimes the diagnosis is established only peroperatively, even postoperatively, after meticulous dissection of the operative specimen.

We present the case of a 38 year old young women who was admitted for palpable epigastric tumor and violent abdominal pains. Echography, scanner, gastroscopy, radiology and laparoscopy could not specify the origin of the tumor. Only laparotomy and histological examination specified the diagnosis of ectopic antropiloric pancreas.

Retrospectively, only the CT could suggest the diagnosis. If the laparoscopy is often named "the queen" of the abdominal exploration, the laparotomy is "the emperor".

EVALUATION OF PANCREATIC EXOCRINE FUNCTION USING MRI IMAGING

A. Nanashima*, H. Yamaguchi, H. Ayabe, T. Fukuda, A. Kuroda.

First Department of Surgery and Department of Radiology, Nagasaki University School of Medicine, Nagasaki, Japan

Introduction. Recent studies have evaluated pancreatic exocrine function by using MRCP to monitor changes in duodenal fluid induced by secretin. However, this method does not provide a quantitative measure of pancreatic exocrine function. We evaluated pancreatic exocrine function by measuring changes in the intensity of pancreatic tissue on MRI.

Patients and Method. We examined five patients with pancreatic exocrine hypofunction confirmed by PFD test (hypo-function group) and five normal volunteers as control group. After intravenous injection of 100 units of secretin (Secrepan, Eisai), T2 enhanced images of pancreatic tissue were serially taken for 16 minutes. The ratio of intensity between pancreas tissue and iliopsoas muscle was calculated and changes in the intensity ratio were calculated in both groups.

Results. In the control group, the intensity ratio increased immediately after injection of secretin and reached a peak value at about 5 minutes. However, the intensity ratio gradually decreased to the baseline value. In contrast, in the hypo-function group, two different patterns were observed: 1) no changes in the intensity ratio relative to baseline value, 2) the intensity ratio gradually increased but the peak value was delayed compared with the control.

Conclusion. Our results showed that the intensity ratio of pancreas tissue in patients with hypo-function of pancreatic exocrine secretion was different from that in normal subjects, and suggest that MRI-secretin method may be useful for quantitative assessment of pancreatic exocrine function. It may also be used for analysis of patients who undergo intestinal reconstruction after pancreaticoduodenectomy.

ACUTE PANCREATITIS - EARLY OR LATE SURGERY ?

A WRONG QUESTION.

S.Neagu, R.Costea, V.Zarnescu, V.Dinca.

Surgical Department, University Hospital, Bucharest, Romania.

Introduction. In the evolution of the surgical treatment of acute pancreatitis (AP) there were two periods: the old period when we recommended early surgery and the late period when we do not operate in the first interval and we operate only when septic complications occurred. In our retrospective study we try to see if the modern concept is sustained by the results in our cases.

Patients and Method. From 1989 to 1995 100 cases of necrotic pancreatitis (NP) were treated in our department. It was 68 male and 32 women. The etiology was biliary in 38 cases, etanolic in 27 cases, metabolic dislipidemic in 12 cases, drugs related in 2 cases and unknown in 21 cases. The lesion involved all the pancreas (total NP) in 32 cases and just a segment (parcelary NP) in 68 cases. All the cases were operated.

Results. The surgery was *early indicated* when the clinic shows an acute abdomen with ascitis and peritonitic syndrome, the etiology was biliary or the choledocian obstruction was important and *later*, in the period of septic intraabdominal complications in the others cases. The explorer laparotomy established the diagnosis and the precise extend of lesions, the imagistic explorations offering sometimes lacunary data. The early surgery realized the biliary decompression and drainage and treatment of the etiological biliary factor, the lavage of the peritoneal cavity, opening and draining the peripancreatic spaces. The late surgery realized the evacuation and drainage of the collections or pancreatic necrectomies, sometimes pancreatic caudal resection. Global mortality was 48%, but only 24% for biliary etiology.

Conclusion. In our mind "early or late surgery" for acute pancreatitis is a wrong concept. The time of surgery is indicate by different factors: etiology, clinic, evolution. In all the cases the surgery in NP must be always conservative regarding the pancreatic tissue.

ENTEROPANCREATIC REFLEXES: INVOLVEMENT OF M1- AND CHOLECYSTOKININ (CCK)-A-RECEPTORS

E. Niebergall-Roth*, S. Teyssen, M. V. Singer

Department of Medicine IV (Gastroenterology), University Hospital of Heidelberg at Mannheim, Germany.

Introduction. The early pancreatic enzyme response to intraduodenal (id.) stimulants is mediated by a vago-vagal cholinergic enteropancreatic reflex (Am J Physiol 1980;238:G23-G29). The aim of the study was to further characterize the cholinergic receptors and to investigate a possible involvement of CCK-A-receptors in this reflex.

Methods. In 6 conscious dogs with gastric and duodenal cannulas, secretin (164 pmol/kg/h iv.) was given to provide a flow of pancreatic juice of about 1 drop/sec. Amylase activity was measured in each drop before and after rapid iv. injection of caerulein (7.4 pmol/kg) or id. injection of L-tryptophan (TRP; 1 mmol), Na-Oleate (3 mmol), and HCl (3 mmol). The experiments were repeated in the presence of the M1-antagonist telencepine (81 nmol/kg iv.) and of the CCK-A-antagonist L-364,718 (0.1 mg/kg iv.). Latency of response was defined as the time elapsing between injection and increase in amylase activity greater than the mean + 3SD of prestimulation output.

Results. Latency of pancreatic amylase response to TRP and oleate was significantly ($p < 0.05$) shorter than to caerulein and to HCl. Telencepine increased the latency to TRP and oleate, but not to HCl. L-364,718 abolished the response to all given stimuli.

Latency (sec.) of amylase response (means $\pm$ SEM)

	Caerulein	Tryptophan	Na-Oleate	HCl
Control (n=6)	28 $\pm$ 4	17 $\pm$ 7*	16 $\pm$ 5*	120 $\pm$ 473*
Telencepine (n=3)	30 $\pm$ 4	173 $\pm$ 138*	220 $\pm$ 119*	127 $\pm$ 70*
L-364,718 (n=3)	> 15 min.	> 15 min.	> 15 min.	> 15 min.

* $p < 0.05$ vs. caerulein; * $p < 0.05$ vs. HCl; $\ddagger p < 0.05$ vs. control

Conclusions. The present study confirms and extends earlier findings: Since the latency of amylase response to TRP and oleate was shorter than to iv. caerulein, the initial response is probably not due to release of hormones into the circulation but rather to a cholinergic reflex ending on muscarinic M1-receptors. However, the activation of (possibly vagal) CCK-A-receptors (possibly by neural or paracrine CCK) is essential for running the reflex. The initial amylase response to HCl is probably mediated by the release of CCK into the circulation.

CANINE CHOLECYSTOKININ (CCK) RESPONSE TO INTESTINAL TRYPTOPHAN IS INDEPENDENT FROM CCK-A-RECEPTORS

E. Niebergall-Roth*, S. Teyssen, R. L. Riepl*, and M. V. Singer

Dept. Med. IV (Gastroenterology), Univ. Hosp. of Heidelberg at Mannheim.

*Univ. Hosp. of Munich, Germany.

Introduction. Blockade of CCK-A-receptors increases human postprandial plasma CCK concentration, possibly by suppressing bile flow into the intestine and thereby counteracting a postulated negative feedback control of CCK-release by bile acids. In dogs, control of CCK-release is unknown.

Methods. In six conscious dogs with gastric and duodenal fistulas we studied the effect of the CCK-A-receptor antagonists *loxiglumide* (LOX; 2.5, 5.0 and 10.0 mg/kg/h iv.) and *L-364,718* (L364; 0.025, 0.05 and 0.1 mg/kg/h iv.) on the plasma CCK-like (radio)immunoactivity (CCK-LI) in response to graded loads of intraduodenal (id.) tryptophan (TRP; 0.37-10.0 mmol/h), given against a background of secretin (20.5 pmol/kg/h iv.). The 180-min integrated CCK response (iCCKr, pmol/l) to all loads of TRP was calculated.

Results. The basal plasma CCK-LI (4.6 $\pm$ 0.5 pmol/l) was not significantly altered by secretin (4.6 $\pm$ 0.4 pmol/l). The higher loads of TRP (1.1-10.0 mmol/h) significantly increased the plasma CCK-LI. Neither LOX nor L364 significantly altered plasma CCK-LI in response to tryptophan (+ secretin).

CCK-LI (pmol/l) in response to TRP and 180-min. iCCKr (pmol/l) in response to all loads of TRP

TRP (mmol/h):	0.37	1.1	3.3	10.0	iCCKr
Control:	4.3 $\pm$ 0.5	5.9 $\pm$ 0.4	7.8 $\pm$ 0.6	9.8 $\pm$ 1.7	364 $\pm$ 101
LOX (2.5 mg/kg/h):	4.8 $\pm$ 1.8	5.5 $\pm$ 1.4	7.0 $\pm$ 1.0	8.4 $\pm$ 1.2	302 $\pm$ 89
LOX (5.0 mg/kg/h):	3.4 $\pm$ 0.4	4.4 $\pm$ 0.4	5.2 $\pm$ 1.2	8.4 $\pm$ 1.0	295 $\pm$ 112
LOX (10.0 mg/kg/h):	3.7 $\pm$ 0.8	4.6 $\pm$ 0.8	6.2 $\pm$ 0.8	7.9 $\pm$ 0.6	307 $\pm$ 64
L364 (0.025 mg/kg/h):	4.4 $\pm$ 0.5	5.9 $\pm$ 1.3	7.3 $\pm$ 1.8	8.2 $\pm$ 1.6	334 $\pm$ 137
L364 (0.05 mg/kg/h):	4.6 $\pm$ 1.6	5.9 $\pm$ 1.8	7.3 $\pm$ 1.2	8.8 $\pm$ 1.6	298 $\pm$ 82
L364 (0.1 mg/kg/h):	4.2 $\pm$ 1.1	6.1 $\pm$ 2.6	7.5 $\pm$ 2.2	9.1 $\pm$ 1.8	314 $\pm$ 200

Results are means $\pm$ SEM (n=6)

Conclusions. In dogs, the CCK-A-receptor antagonists LOX and L364 - even in the highest doses which have earlier been shown the cause a total CCK-A-receptor blockade - are not capable of altering the CCK-response to id. TRP. Thus, the canine postprandial CCK-release is controlled at least in part by a mechanism (e. g. cholinergic nerves) which is independent from CCK-A-receptors.

DIFFERENT ROLE OF M1-RECEPTORS IN THE MEDIATION OF ENDOGENOUSLY VERSUS EXOGENOUSLY STIMULATED PANCREATIC ENZYME OUTPUT IN DOGS.

E. Niebergall-Roth*, S. Teyssen, and M. V. Singer

Department of Medicine IV (Gastroenterology), University Hospital of Heidelberg at Mannheim, Germany.

Introduction. It is still disputed if all action of cholecystokinin (CCK) on pancreatic exocrine secretion is mediated via cholinergic nerves or if CCK acts at least in part independently of cholinergic nerves.

Methods. In six conscious dogs with gastric and duodenal fistulas we compared the effect of the M1-receptor antagonist telencepine (20.25, 40.0 and 81.0 nmol/kg/h iv.) on the pancreatic protein response to graded doses of intraduodenal tryptophan (0.37-10.0 mmol/h) and of intravenous caerulein (7.4-188.0 pmol/kg/h) given against a background of secretin (20.5 pmol/kg/h iv.). The incremental protein output (observed protein output to each tryptophan load and caerulein dose, respectively, given with secretin minus the response to secretin alone) was calculated.

Results. Both caerulein and tryptophan dose-dependently increased the pancreatic protein output over that seen with secretin alone. Telencepine significantly ($p < 0.05$) decreased the incremental protein responses to the lower loads (0.37-3.3 mmol/h) of tryptophan by up to 96 %, but did not alter the pancreatic protein response to the highest load (10.0 mmol/h) of tryptophan. In addition, telencepine did not affect the protein response to any dose of caerulein.

Conclusions. In contrast to endogenous stimulation with low loads of tryptophan, high doses of tryptophan and exogenous caerulein stimulate pancreatic protein output without being affected by the M1-antagonist telencepine. Thus, endogenously released CCK may control pancreatic enzyme secretion at least in part independently from cholinergic M1-fibers. The cholinergically independent pathway is mainly important for CCK released by high loads of tryptophan.

QUANTITATIVE ANALYSIS OF SIALYLATED LEWIS ANTIGEN AND GLYCOSYLTRANSFERASE GENE EXPRESSION OF PANCREATIC CANCER

S. Nishihara¹, T. Hiraga¹, Y. Ikehara¹, T. Kudo¹, S. Nakamori².

K. Morozumi³, H. Narimatsu¹

Division of Cell Biology, Institute of Life Science, Soka University¹

Department of Surgery, Osaka University Medical School²

Division of Surgery, Hussa Hospital³

Introduction. The carbohydrate antigens in pancreatic cancer tissue dramatically change in comparison with those normal tissue. The CA19-9 epitope (sLe^a), one of the sialylated Lewis antigens, is well known tumor marker which is useful for screening of cancer in pancreas, colon and other organ. The sLe^a and sLe^x antigens are known to serve as ligands for selectin molecule and considered to participate in the via E-selectin to venular endothelium *in vivo* which is the essential step for cancer cell metastasis. In an attempt to correlate the sialylated Lewis antigen expression in human pancreatic tissue with expression of glycosyltransferase genes, we quantitatively analyzed glycosyltransferase transcripts in pancreatic cancer.

Methods. 1) We established the competitive RT-PCR method for measuring eleven kinds of glycosyltransferases, which were considered to be involved in the synthesis of sialylated Lewis antigens, and applied for pancreatic cancer. 2) The amounts of sLe^a, sLe^x and Le^b antigens were determined by Western blotting analysis using anti-sLe^a, sLe^x and Le^b mAb, respectively. 3) Genotyping of two glycosyltransferases, Lewis enzyme and Se enzyme were performed by PCR-RFLP method.

Results and conclusion. 1) The sLe^a, sLe^x and Le^b antigens increased dramatically in cancer. The correlation between the amount of sLe^a and that of sLe^x was observed. 2) The sLe^a expression was influenced by Lewis genotype. Lewis enzyme synthesized sLe^a antigen. 3) The Se enzyme expression was in good proportion to the amounts of Le^b antigens to show that Se enzyme synthesizes Le^b antigens. But the amounts of sLe^a and sLe^x antigens did not correlate directly with four α 2,3-sialyltransferase (ST3GalII, III and IV) transcripts, three α 1,3-fucosyltransferase (Lewis enzyme, Fuc-TIV, Fuc-TVI) transcripts, β 1,4-galactosyltransferase (β 1,4Gal-T) transcripts and Core 2 β 1,6-N-acetylglucosaminyltransferase (Core 2 GaT) transcripts.

SPECIFIC INHIBITION BY PEITC OF INITIATION PHASE OF BOP-PANCREATIC TUMORIGENESIS IN THE HAMSTER

A. Nishikawa, F. Furukawa, K. Kasahara, T. Imazawa, M. Takahashi.

Division of Pathology, National Institute of Health Sciences, Tokyo, Japan

Introduction. Phenethyl isothiocyanate (PEITC), a natural constituent of cruciferous vegetables, has been extensively investigated for its cancer chemopreventive activity in rodents. In the present study, the effects of PEITC on pancreatic tumorigenesis induced by *N*-nitrosobis(2-oxopropyl)amine (BOP) in hamsters were investigated separately in the initiation and post-initiation phases.

Materials and Methods. Female 5-week-old Syrian hamsters were twice given subcutaneous injections of BOP 7 days apart at a dose of 20 mg/kg body weight as an initiation treatment. Groups 1 and 2 received either 100 or 10 μ mol PEITC per animal by gavage, 2 h prior to each BOP treatment. Groups 3 and 4 were fed a diet supplemented with PEITC at a dose of 6 or 3 μ mol/g for 51 weeks after the second BOP treatment. Group 5 and 6 animals respectively served as BOP-positive and non-treatment controls. At the end of week 52, all surviving animals were killed and histopathologically examined for the existence of pancreatic proliferative lesions.

Results. Cancerous and precancerous ductal lesions of the exocrine pancreas were respectively diagnosed as adenocarcinomas and dysplastic lesions. These lesions were found in Groups 1-5 but not in Group 6. The combined multiplicity of adenocarcinomas and dysplastic lesions in Group 1 was significantly ($p < 0.01$) decreased as compared to the Group 5 value. However, the incidences and multiplicities of these lesions in Groups 3 or 4 were essentially comparable with Group 5, even showing a tendency for increase.

Conclusion. Our results clearly indicate that PEITC is specifically effective against BOP-induction of pancreatic tumorigenesis in hamsters when given in the initiation phase.

DIFFERENTIAL EFFECT OF NITRIC OXIDE SYNTHASE INHIBITORS ON EXPERIMENTAL PANCREATITIS IN THE RAT

T. Nishino, S. Watanabe, H. Oyama, Y. Fukuya, K. Shiratori,

N. Hayashi and M. Kobayashi.

Dept of Gastroenterology and Int. Med., 1st Dept of Pathology*, Tokyo Women's Medical College, Tokyo, Japan

Introduction. Nitric oxide (NO) has been reported to contribute to multiorgan oxidative stress and tissue injury in Na-taurocholate induced pancreatitis, but some investigators have reported finding that NO has a protective effect in cerulein-induced pancreatitis. To clarify the significance of NO in acute pancreatitis, we investigated the effect of different NO synthase inhibitors and NO donors on experimental pancreatitis.

Methods. Closed duodenal loop (CDL)-induced pancreatitis was produced in male Wistar rats and the animals were divided into five groups: 1) NS group: infusion of normal saline; 2) ARG group: NOS substrate, L-arginine (25 mg/kg bolus followed by 5 mg/kg/h); 3) SNAP group: NO donor, S-nitroso-N-acetyl-penicillamine (0.2 mg/kg/h); 4) AG group: iNOS inhibitor, aminoguanidine (20 mg/kg followed by 5 mg/kg/h); 5) L-NAME group: the more powerful inhibitor of eNOS than iNOS, N-nitro-L-arginine methyl ester (10 mg/kg followed by 2.5 mg/kg/h). All drugs were infused intravenously during a period of 6 h or 12 h in 10-12 animals in each group. Pancreatic tissue was removed at 6 h and 12 h after creating the CDL.

Results. Serum amylase levels were increased 3 h after creating the CDL. L-NAME-treated animals showed significantly increased serum amylase levels compared to the animals in the NS, ARG, SNAP and AG group every time 3 h onwards. Histologically, L-NAME administration significantly increased edema and acinar cell vacuolization at 6 h and resulted in severe hemorrhage and acinar cell necrosis than observed in the other four groups at 12 h. Neither ARG, SNAP nor AG had any significant effect on the histological changes.

Conclusions. The eNOS inhibitor significantly aggravated pancreatitis, but NO donors or iNOS inhibitor did not change the severity of the pancreatitis. We conclude that eNOS may play a protective role against the progression of acute pancreatitis.

TRYPSINOGEN GENE MUTATION IN JAPANESE FAMILIES WITH HEREDITARY PANCREATITIS

I. Nishimori^{*1}, M. Kamakura¹, K. Adachi¹, M. Morita¹, S. Onishi¹, and S. Watanabe², and M. Ogawa³

¹First Dept. of Internal Medicine, Kochi Medical School, Kochi, Japan.

²Institute of Gastroenterology, Tokyo Women's Medical College, Tokyo, Japan.

³Dept. of Surgery II, Kumamoto Univ Medical School, Kumamoto, Japan.

Introduction. Single-point mutations in the cationic trypsinogen (CT) gene have been reported in Caucasian hereditary pancreatitis (HP) kindreds. We studied CT and anionic trypsinogen (AT) gene mutations in Japanese HP kindreds.

Methods. All five exons of the CT and AT genes were amplified by PCR and sequenced in seven Japanese HP families.

Results. Two kinds of a single-point mutation in the CT gene, which were identical to those previously reported in Caucasian HP families, were observed in separate Japanese HP families:

²⁹Asn(AAC):Ile(ATC) in exon 2 and ¹²²Arg(CGC):His(CAC) in exon 3. Pancreatitis occurred at more advanced ages in patients with the N29I mutation than patients with the R122H mutation. Large calcified pancreatic stones were observed in patients with the N29I mutation, but small stones were observed in only one of three patients with the R122H mutation. Besides normal polymorphisms in exons 4 and 5 of the CT gene and in exon 3 of the AT gene, no mutation was found in patients in the remaining 5 HP families, 21 patients with sporadic chronic pancreatitis, and 5 normal subjects.

Conclusions. These results show the heterogeneity, but no racial specificity, in the CT gene mutations in HP kindreds. Distinctive clinical features for each of the mutation types were suggested: adult onset and large calcified pancreatic stones for the N29I mutation, and childhood onset and no tendency toward pancreatic calcification for the R122H mutation.

PROGRESSION TO MUCIN PRODUCING TUMOR AND PANCREATIC DUCTAL ADENOCARCINOMA FROM INTRADUCTAL TUMOR OF THE PANCREAS

B. Nobukawa^{*1}, K. Suda, H. Fujii², Y. Matsumoto.

¹First Department of Pathology, Juntendo University Hospital,

Tokyo, Japan. ²First Department of Surgery, Yamanashi Medical University, Yamanashi, Japan.

Introduction. Most of exocrine pancreatic tumors which have been diagnosed today are either mucin producing tumor (MPT) or pancreatic ductal adenocarcinoma (PDA). We attempted to clarify the morphological and biological differences between both tumors.

Patients and Methods. Intraductal component and invasive component were identified by means of hematoxylin-eosin stain and elastica van Gieson (E.V.G.) stain in 20 MPT and 25 PDA surgical specimens. Furthermore, expression of MUC1 (DF3, DAKO) and MUC2 (Ccp58, Novocastra) were examined by immunohistochemistry in both components.

Results. Immunohistochemistry as shown in following table.

	intraductal component		invasive component	
	MUC1	MUC2	MUC1	MUC2
Mucus cell hyperplasia	-	-		
Atypical hyperplasia	-	+		
Intraductal papillary adenoma	-	+		
adenocarcinoma				
non-invasive	-	+		
minimally invasive	-	+	-	+
invasive	++	++	++	++
Ductal adenocarcinoma	+	-	+	-

Conclusion. Although both MPT and PDA arise as intraductal tumor of the pancreas, they acquire different malignant biological characters in different sequences of the carcinogenetic progression and natural course: MPT acquires expansive growth with MUC2-positive immunoreactivity but remaining in situ with duct dilatation, filling with copious mucin, and PDA acquires immediate invasive growth into the stroma with MUC1-positive immunoreactivity.

CLINICAL STUDIES OF PANCREATIC DISORDERS IN LOW FLOW SYNDROME - ISCHEMIC PANCREATITIS ?

A.Noda, H.Murayama, S.Hase, E.Ibuki, K.Takeuchi, T.Suga
Third Department of Internal Medicine, Aichi Medical University
Introduction. Controversies exist concerning the role of vascular factors in pathogenesis of pancreatitis. We investigated pancreatic disorders in patients of low flow syndrome caused by cardiovascular diseases.

Patients and Methods. Of patients who were admitted to Aichi Medical University Hospital suffering from cardiovascular emergencies, eight patients were selected for the present studies: male in six, female in two and 24-93yrs (mean 67.8yrs). Basic cardiovascular diseases were as follows: acute myocardial infarction(AMI) in two, old myocardial infarction(OMI) in two, AMI or OMI plus aorta aneurysm of the abdomen (AAA) in two, viral myocarditis in one and acquired valvular disease in one. No patients had any known pancreatic diseases. Serum amylase and its isozyme were measured in all patients.

Results. 1. Serum amylase was elevated in all patients, ranging from 1,027 to 8,371 mU/ml (normal <400mU/ml), and a pancreatic-type isoamylase was dominant. 2. Upper abdominal or epigastric pain was noted only in two patients. Seventy of pancreatitis, which was assessed by using the recent criteria, was mild and moderate in each patient. 3. Five patients had been in shock on their admission to ICU, so that it was obscure whether they had had any complaints related to pancreatitis. 4. Three patients died of the rupture of AAA, heart failure or multiple organ failure(MOF). The other patients recovered from pancreatitis. 5. Autopsy was done in 93yo male patient who had suffered from diabetes mellitus, OMI and AAA, and died of MOF. Hyperamylasemia and inflammatory response were persistent. Histopathology of the pancreas revealed acute deterioration of chronic pancreatitis and severe arteriosclerosis of intra- and extrapancreatic arterioles.

Conclusion. Ischemic pancreatitis may occur in the low perfusion to the pancreas.

REFERENCE VALUES OF URINARY TRYPSINOGEN ACTIVATION PEPTIDE AND PROPHOSPHOLIPASE A₂ ACTIVATION PEPTIDE

K. Ochi, M. Ichimura, T. Mizushima, H. Harada, H. Hasuoka¹⁾
Department of Laboratory Medicine, Okayama University Medical School & Katsuyama Hospital¹⁾, Okayama, Japan

Introduction. Trypsinogen activation peptide (TAP) and phospholipase A₂ activation peptide (PROP) are reported as useful markers for severe acute pancreatitis or multiorgan failure. However, few studies have done large-scale studies on the effect of sex & age on reference values.

Patients and Methods. Urinary levels of TAP and PROP were studied using 380 subjects without pancreatic diseases. TAP and PROP were assayed by ELISA kits (Oriental Yeast Co Ltd., Tokyo).

Results. Tap values showed no sex- and age-related difference, whereas PROP showed higher values in females (n=216) than in males (n=164) with no age-related difference (135 subjects ≤65 years vs. 245 >65 years). No significant correlation was noted between TAP and PROP values. TAP and PROP values showed Gaussian distribution after logarithmic conversion. Reference values were set by Hoffmann's iterative truncation method. Upper limit of normal was 8.2 nM for TAP, whereas that for PROP was 7.7 nM in males with 9.3 nM in females.

Conclusion. Upper limit of normal was age-unrelated and set for urinary TAP and PROP. PROP was higher in females.

ORAL LITHOLYSIS AND ELIMINATION OF CALCIFIED PANCREATIC STONES AND PROTEIN PLUGS

A.Noda, S.Hase, E.Ibuki, K.Takeuchi, H.Murayama, T.Suga
Third Department of Internal Medicine, Aichi Medical University
Introduction. Intraductal pancreatic stones and protein plugs act as an outflow barrier of pancreatic secretion, and can induce recurrent attacks of abdominal pain and progress chronic inflammation of the pancreas.

Patients and Methods. Thirty six patients were selected for the present studies: 34 with calcified pancreatic stones (alcoholic in 22), one with protein plugs(nonalcoholic), and one with recurrent attacks of pancreatitis after pancreatoduodenectomy. The anti-epileptic agent trimethadione(TMO) and the mucolytic expectorant bromhexine -HCl were given orally at a dose of 0.6-1.2g daily to patients with calcified stones, and at a dose of 12mg daily to the other patients, respectively. Another 30 patients with calcified stones served as a TMO-nontreated(control) group. Pancreatic stones, protein plugs and clinical features of patients were followed up for 14-148 months.

Results. 1. On plain X-ray films and CT scans of the abdomen, calcified stones diminished in size and number or disappeared in 23 patients(68%). Impaired exocrine pancreatic function returned to normal in one-third of patients, and diabetes mellitus was well controlled by either diet therapy alone or oral hypoglycemic agents in 63% of patients. Complete relief of pain was noted in 78% of patients. Overall gains and no change in body weight were observed in 83% of patients. 2. Pancreatic stones of the control group neither disappeared or diminished spontaneously. 3. Administration of bromhexine-HCl eliminated protein plugs and relieved recurrent attacks of pancreatitis.

Conclusion. TMO treatment is a useful tool for chemical litholysis of calcified pancreatic stones. Bromhexine-HCl has a potential to eliminate protein plugs and relieves an attack of pancreatitis, resulting probably from decreasing viscosity of pancreatic juice.

CA 19-9 AS A PROGNOSTICATOR IN THE TREATMENT OF PANCREAS CANCER BY PREOPERATIVE RADIOTHERAPY (RT)

^aK. Ohara*, ^aN. G. Molotkova, ^aW. Shimizu, ^aY. Saida, ^bT. Oda, ^bT. Todoroki, ^bK. Fukao, ^aY. Itai.
Departments of ^aRadiology and ^bSurgery, University of Tsukuba Hospital, Tsukuba City, Japan

Introduction. We have been treating patients with potentially localized pancreas cancers with preoperative RT; this treatment setting could improve resectability and yet eliminate patients with occult metastasis. CA 19-9 is a tumor marker available for estimating active tumor cell burden. We studied usefulness of CA 19-9 in this treatment setting.

Patients and Methods. We used 23 pancreas cancer patients with elevated CA 19-9, treated by preoperative RT (30-50 Gy) between 1991 and 1997. They were planned to be followed by tumor resection when possible and intraoperative radiotherapy (IOR, 20 Gy) irrespective of resection. CA 19-9 serum level was checked before RT, immediately after RT, and thereafter. Recurrence including liver or peritoneal metastasis and local progression was determined with CT scans to study the relationship with changes of CA 19-9.

Results. CA 19-9 level before RT, ranged from 64 to 14000 U/ml, decreased immediately after RT in 10 patients (Group A), increased in 10 patients (Group B), and remained stable in 3 patients (Group C). In Group A, 6 patients underwent laparotomy: IOR alone (4 pts: one showed peritoneal dissemination), resection+IOR (1 pt), resection alone (1 pt); and 4 patients did not: estimated unresectable (3 pts) and metastasis (1 pt). In Group B and C, 6 patients underwent laparotomy: IOR alone (4 pts), resection -IOR (1 pt), resection alone (1 pt); and 7 patients did not: estimated unresectable (2 pts) and metastasis (5 pts). Metastasis developed by 60 days after the initiation of RT in these 7 patients. Metastasis developed thereafter in 15 of remaining 16 patients. Initial recurrence was liver metastasis (14 pts), peritoneal dissemination (7 pts) and pleural dissemination (1 pt). Time of recurrence ranged from 30 to 272 days (mean, 150.4) in Group A and from 35 to 348 days (mean, 116) in Group B and C. Prior to clinical recurrence CA 19-9 level increased in 17 (77.3%) of 22 patients. Median survival of all patients was 265.8 days. The surgically treated patients survived longer than non-surgically treated patients: 312 vs. 214 days (p<0.05). The patients of Group A and Group B and C who underwent surgery survived 327 and 299 days, respectively (NS).

Conclusion. Monitoring of CA 19-9 level before and immediately after preoperative RT is useful in predicting early development of metastasis in patients with clinically localized pancreatic cancer at presentation.

A NEW RECONSTRUCTIVE METHOD FOR PANCREATOCODUODENECTOMY WITH GASTRECTOMY. RECONSTRUCTION WITH GASTRO-JEJUNAL POUCH ANASTOMOSIS.

N. Ohashi, H. Tamaki, T. Sanda, K. Kawamura, M. Iwata, M. Kume, K. Hamada, K. Tanaka

Dept. Surg, Matsusaka Chuo Hospital, Matsusaka, Japan

Introduction. Pylorus preserving pancreaticoduodenectomy (PpPD) is a standard operation for peripancreatic neoplasms, however, pancreaticoduodenectomy (PD) accompanied with gastrectomy is still recommended for some malignant diseases. Malnutrition is one of important complications after PD, especially with gastrectomy, our new reconstructive method after PD could improve the oral nutrition after surgery. **Case report.** A 54-year-old male was admitted to our hospital complaining of abdominal fullness and vomiting after eating. Borrmann type-2 gastric carcinoma was recognized in the antrum of the stomach. On operation, a tumor was exposed on the anterior surface of the stomach and nodal metastases were positive also in the nodes along ASPDA and SMV. En bloc pancreaticogastroduodenectomy and extended lymphnode dissection of nodes around SMV and hepatoduodenal ligament was performed. Pancreaticojejunostomy and choledocojejunostomy was performed with interpositioned jejunum. Jejunal pouch was made with cutting the wall of the jejunal loop and was anastomosed with residual stomach. Oral intake was started at 9th post op and he could take 70% of usual food at 24th post op. His weight gained to +1kg at 40th post op. **Conclusion.** Jejunal pouch anastomosis with the residual stomach after PD with gastrectomy could improve oral intake.

THE RAS-RELATED SMALL GTP-BINDING PROTEIN RAB4 IS INVOLVED IN REGULATED EXOCYTOSIS OF RAT PANCREATIC ACINI

Hirohide Ohnishi*, Tetsuya Mine, Tomohiro Tsuchida, and Toshiro Fujita

Department of Internal Medicine IV, University of Tokyo School of Medicine, Tokyo, Japan.

Introduction. Rab4, a member of the Rab family of Ras-related small GTP-binding proteins, has recently been suggested to participate in exocytosis in addition to its well known role in recycling of GLUT4 and transferrin receptors. The present study was conducted to elucidate the function of Rab4 in regulated exocytosis.

Methods and Results. Western blotting showed Rab4 to be localized to zymogen granule membranes of pancreatic acini as well as to endosome rich fraction. When the synthetic peptide corresponding to the Rab4 hypervariable carboxyl-terminal domain was introduced into streptolysin-O permeabilized acini, the amylase release induced by 10 μ M free calcium was potentiated by 80% at maximum in a concentration-dependent manner. Furthermore, anti-Rab4 antibody enhanced calcium-triggered amylase release from permeabilized acini. To further elucidate the involvement of Rab4 in the stimulus-secretion coupling, we examined the effect of CCK on GTP-binding rate to Rab4. GTP-binding rate was measured by introducing radiolabelled GTP into streptolysin-O permeabilized acini and immunoprecipitating GTP-bound Rab4. Stimulation of pancreatic acini with 100 pM CCK increased the incorporation of radiolabelled GTP into Rab4 by 75% compared to control. TPA also enhanced the GTP-binding rate to Rab4 in pancreatic acini. In addition, pretreatment of pancreatic acini with 1 μ M calphostin C, a protein kinase C inhibitor, attenuated the stimulatory effect of CCK on GTP-binding to Rab4.

Conclusion. Rab4 protein on zymogen granules plays a crucial role in regulated exocytosis and that Rab4 is involved in the stimulus-secretion coupling of pancreatic acini via protein kinase C dependent signalling pathway

EFFECTS OF HEPATOCYTE GROWTH FACTOR AND TRANSFORMING GROWTH FACTOR α ON THE GROWTH OF HUMAN PANCREATIC CANCER CELL LINES

N. Ohba, R. Makino, T. Seki, H. Funatomi*, K. Mitamura
Second Department of Internal Medicine, Showa University School of Medicine, Tokyo, Japan

Introduction While mitogenic effect of transforming growth factor α (TGF α) on human pancreatic cancer is well known, the role of hepatocyte growth factor (HGF) on the development of pancreatic cancer is not yet enough evaluated. We investigated the effects of HGF and combined treatment with TGF α on the growth of human pancreatic cancer cells.

Methods Panc-1, COLO 357, T3M4 and ASPC-1 human pancreatic cancer cell lines were used. These cells were plated on a 96 well plate and medium was changed to serum free medium supplemented with TGF α or HGF at concentrations up to 20 ng/ml. Fixed concentration (10 ng/ml) of HGF was combined with different concentrations of TGF α . Cell growth was assessed by MTT assay 48 hours after medium change.

mRNA expression of c-met, TGF α and epidermal growth factor receptor after treatment of each cells with TGF α or HGF was examined by Northern blotting using respective cDNA probes.

Results TGF α stimulated the cell growth of all cell lines. The stimulatory effect of HGF on cell growth was observed in COLO 357, T3M4 and ASPC-1 cells, except for Panc-1 cells. Combination treatment with 10 ng/ml of HGF and 1 ng/ml of TGF α enhanced their stimulatory effect compared to HGF alone. However, this effect was not clearly shown when the concentration of TGF α was increased to 10 ng/ml.

In all cell lines, treatment with TGF α increased the expression of TGF α mRNA and treatment with HGF did not influence the expression of c-met mRNA. In ASPC-1 cells, expression of TGF α mRNA was enhanced by the treatment with HGF.

Conclusion HGF stimulated human pancreatic cancer cell growth except for Panc-1 cells and combination treatment with a low dose of TGF α enhanced its stimulatory effect, but combination of high dose did not. TGF α mRNA expression was enhanced by HGF in ASPC-1 human pancreatic cancer cells.

THE STRATEGY FOR SEVERE ACUTE PANCREATITIS —ARTERIAL INFUSION OF PROTEASE INHIBITOR AND ANTIBIOTICS—

T. Okada, H. Komoriyama, M. Hagiwara, S. Kubota*, S. Yamaguchi*

Dept. of Surgery, St. Marianna Univ., Yokohama City Seibu Hospital,

*First Dept. of Surgery, St. Marianna Univ., Kawasaki, Japan

Introduction. The protease inhibitor (PI) have been studied closely as very promising drugs for acute pancreatitis. However, studies have failed to show the effectiveness of these inhibitors. We have been obtaining favorable results by performing continuous arterial infusion of PI during pancreatitis, and the present with these findings.

Patients and Method. We have performed continuous arterial infusion of protease inhibitor and antibiotics (CAPI) on twenty-six patients with severe acute pancreatitis. Depending on the location of the pancreatitis as determined on dynamic CT scan, the tip of catheter was placed at the point where the bloodstream irrigated the inflamed area of the pancreas. Thereafter nafamostat mesilate 240mg/d, in combination with the antibiotics imipenem 1g/d, was continuously infused for five consecutive days.

Results. After CAPI, clinical signs and symptoms such as abdominal pain had improved, with amelioration of biochemical parameters.

Angiography revealed improvement of pancreatic blood flow that was insufficient before CAPI. The survival rate was 92.3% (24/26). Surgical extirpation was performed in three cases.

Conclusions. CAPI in severe acute pancreatitis was effective in reducing mortality and preventing the development of necrotic lesions.

NEUROTROPHIC FACTOR DERIVED INVASION OF PANCREATIC CANCER

Y. Okada, H. Takeyama, M. Sato, T. Manabe

First Department of Surgery, Nagoya City University Medical School, Nagoya, Japan

Introduction. Perineural invasion is a prominent clinical feature of pancreatic cancer, and causes a difficulty of curative resection.

Methods and result. In this study, all currently used human pancreatic cancer cell lines, PaCa-2, AsPC-1, SW1990 and Capan-2, were found to express an abundant c-ret proto-oncogene and ret protein which were identified to be a receptor for glial cell line-derived neurotrophic factor (GDNF) as a member of receptor tyrosine kinase superfamily. In the invasion assay, the migration of pancreatic cancer cell was markedly induced by a cocultivation with human glioma cells, T98G or A172, capable of producing GDNF and its extracellular secretion. Anti GDNF antibody could suppress a majority of the migratory activity, but not all, in the conditioned media of glioma cells. Checker board analysis on the migration showed both chemotactic and chemokinetic activity of GDNF. Immunohistochemical localization of GDNF in human celiac ganglionic tissue attested to the contention.

Conclusion. The specific neural invasion of human pancreatic cancer cell expressing a c-ret proto-oncogene spreads along a concentration gradient of GDNF produced from peripheral ganglions.

IMMUNOLOGICAL ANALYSIS OF AUTOIMMUNE-RELATED CHRONIC PANCREATITIS

K. Okazaki, K. Uchida, T. Chiba, Department of Gastroenterology and Hepatology, and Endoscopy, Kyoto University, Kyoto, Japan.

M. Ohana, H. Takakuwa, K. Hagiwara, Tenri Hospital, Nara, Japan.

Introduction. An autoimmune mechanism may be involved in some patients with idiopathic chronic pancreatitis. However, the clinical features and pathophysiology are still unknown. To clarify it, we analyzed 38 patients with autoimmune-related chronic pancreatitis. **Patients and Methods.** Thirty-eight patients with autoimmune-related pancreatitis were diagnosed as follows: (1) increased pancreatic enzymes, pancreatic exocrine dysfunction, and abnormal pancreatogram, (2) hyper-gammaglobulinemia, autoantibodies, or complication with other autoimmune diseases, (3) histopathologically, infiltration of lymphocytes, (4) effective steroid therapy. In 38 patients (26 males and 12 females, mean age: 63 yr.) with autoimmune pancreatitis, we analyzed clinical features, ERCP images, biochemistry, and immunological findings. We studied autoantibodies (against DNA, smooth muscle, mitochondria, lactoferrin, carbonic anhydrase II, or rheumatoid factor), immuno-histochemistry, or flow-cytometry. **Results.** Fourteen of 38 patients had jaundice. Seven patients were complicated with sicca syndrome, 5 with primary sclerosing cholangitis, and 14 with diabetes mellitus. All patients showed segmental or diffuse stenosis of the main pancreatic duct. Fifteen patients showed stenosis of the common bile duct. BT-PABA excretion test showed abnormal pancreatic exocrine function in 16 patients. Twenty-four patients had hyper-gammaglobulinemia. Rheumatoid factor was detected in 4 of 11, antinuclear antibody in 4 of 12, anti-smooth muscle antibody in 2 of 7, anti-carbonic anhydrase II antibody in 3 of 9, and anti-lactoferrin antibody in 3 of 6. None had anti-mitochondrial antibody. Microscopic findings showed infiltration of CD4(+) lymphocytes around the pancreatic duct, and HLA-DR was expressed on CD4(+) cells and pancreatic duct cells. Flowcytometric analysis confirmed activated T cells were the major infiltrating lymphocytes in the pancreas, more than 80%. **Conclusion.** An autoimmune mechanism against carbonic anhydrase II or lactoferrin via CD4 positive cells may be involved in patients with immune-related chronic pancreatitis.

IMAGING AND GENETIC CHARACTERISTICS OF SMALL NONFUNCTIONAL ISLET CELL TUMOR (NICT)

T. Okaj, K. Ohtsubo, Y. Yamaguchi, H. Watanabe, Y. Morio and N. Sawabu
Department of Internal Medicine, Cancer Research Institute, Kanazawa University, Kanazawa, Japan

INTRODUCTION: Early recognition of NICT is difficult particularly when its size is small and angiography fails to prove tumor staining. We present 3 patients with NICT with their modern imaging modalities and genetic analyses. **PATIENTS AND METHODS:** Three consecutive patients with NICT were enrolled. A patient (A, 55/m) had a back pain occurred two months before, while the other two (B, 43/m; C, 42/f) were asymptomatic. Patient A visited our clinic with the abnormalities such as elevated serum CEA, CA19-9, amylase and elastase 1. Patient B & C were referred for the examination of pancreatic masses incidentally detected by screening US, CT, MRI, EUS, ERCP, and celiac angiography were performed in all. Endoscopically pure pancreatic juices (PPJ) were collected. Mutations of K-ras gene at codon 12 in PPJ were analyzed using HPA. All underwent distal pancreatectomy with splenectomy. Pathological study in patient A showed two malignant NICT (1.4 cm and 1.5 cm in diameter). Patient B was also diagnosed as malignant NICT (3 cm), whereas patient C was diagnosed as benign (8 mm). **RESULTS:** US showed isoechoic tumor with low echoic halo in all. In the malignant NICT the halo was thick and the margin was irregular, whereas the halo was thin and the margin was smooth in the benign NICT. EUS showed almost the same appearance as that of conventional US. However, the images were vivid and their qualities were much more excellent. Dynamic CT study showed faint enhancement in all. MRI in patient A & B showed low intensity in T1 and high in T2, while both T1 and T2 images showed hypo intensity in patient C. Dynamic MRI showed early stain in all. ERCP showed segmental stenosis only in patient A. No tumor stains were detected in celiac angiography. Mutation of K-ras in PPJ was seen only in patient B. **CONCLUSIONS:** Early diagnosis of NICT may be accomplished if its characteristic ultrasound features and hypervascular nature can be proved by imaging modalities. The mutation of K-ras was shown in a patient with malignant NICT, suggesting its chimera character.

TREATMENT OF PANCREATIC STONES BY EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY (ESWL)

K. Okushima, S. Nakazawa, J. Yoshino, K. Inui, Y. Nakamura and T. Takashima

Department of Internal Medicine, Second Teaching Hospital, Fujita Health University, School of Medicine, Nagoya, Japan

Introduction. We performed ESWL to 35 patients with pancreatic stones in the main pancreatic duct (MPD), and evaluated its therapeutic value.

Patients. 29 patients were male and 6 female ranging between 22 and 72 years of age, average 49 years. Pancreatic stones were detected at the following regions of the pancreas: at the head of the pancreas in 27 patients, at the head and body in 4, at the body in 2, and throughout the entire pancreas in 2. Solitary stone were detected in 19 patients, while multiple stones were detected in 16 patients. Maximal diameters of the stones in respective cases ranged between 4-25mm (average 13mm).

Method. The lithotripter used in this study was a Tripter X-1 (Direx Co., Ltd.). Frequency of treatment was 1-18 times (average 4 times), and the number of shock waves ranged from 1,800-31,774 (average 10,424). 18 patients were treated with ESWL only, while other 17 patients were treated by a combination of ESWL and endoscopic therapy.

Results. Stones in the MPD had disappeared in all cases. After treatment, pain disappeared in 36% of the patients. Serum amylase levels decreased after treatment, and the dilatation of the MPD was improved. Values of the PFD test were improved in 2 of 9 patients whose courses were observed for more than 1 year after treatment. Results of oral glucose tolerance test using 75g of glucose became normal in 1 of 6 patients who showed diabetic glucose tolerance before treatment. The insulinogenic index (Δ IRI/ Δ BS) was improved from 0.22 to 0.87 in one patient. Recurrent stones were observed in 6 patients (17%). The rate of recurrent stones detected in 6 patients with stenosis of the MPD was as high as 50%.

Conclusion. ESWL is a useful method of treating pancreatic stones in the MPD. Stenosis of the MPD was thought to promote recurrence of stones.

EVALUATION OF OXYGEN RADICAL PRODUCTION AND EFFECT OF SCAVENGER USING PANCREATIC ISCHEMIA/REPERFUSION MODEL

Ken ONO, Shigeru KOBAYASHI, Kazuhiro SAKAMOTO, Fuyumi ISAYAMA, Mitsuhiro MATSUDA, Atsushi OKUZAWA, Toshiki KAMANO, Masahiko TSURUMARU, Kazuhisa IWABUCHI and Isao NAGAOKA

First Department of Surgery and Department of Biochemistry, Juntendo University School of Medicine

Introduction. It has been proposed that the ischemia/reperfusion injury takes a part in the graft failure after pancreatic transplantation. The aim of this experimental study was to investigate the involvement of oxygen radicals by neutrophil and the effect of scavengers such as superoxide dismutase and catalase using rat pancreatic ischemia/reperfusion injury model.

Material and Method. Male Wistar rats weighing 250-300g were used for the ischemia/reperfusion model. The gastroduodenal artery was clamped for 90 minutes in each model. Local blood flow of the pancreas, serum lipase level, serum amylase level and neutrophil oxygen radical activity were measured after 90 minutes of ischemia followed by 15, 60 or 120 minutes of reperfusion. Scavengers were also administered, and the effects were examined.

Results. Blood flow was almost completely recovered after ischemia/reperfusion. Serum enzyme levels were normal at 15 and 60 minutes of perfusion, however, they increased at 120 minutes after reperfusion. Pancreatic injury was also recognized by electron microscope at the same time when serum enzymes increased. In contrast, the activity of neutrophil oxygen radicals already increased at 15 minutes of reperfusion. The administration of scavengers suppressed the increase in serum pancreatic enzyme levels and activity of neutrophil oxygen radicals. Furthermore, scavengers prevented the pancreatic injury.

Conclusions. The present study demonstrated that the pancreatic ischemia/reperfusion induces oxygen radical generation by neutrophil after early period of reperfusion. In addition, the administration of scavenger seems to be useful for the prevention of pancreatic injury after ischemia/reperfusion.

INHERITED SUSCEPTIBILITY TO ALCOHOL-INDUCED BUT NOT GALLSTONE ACUTE PANCREATITIS

K.-J. Palmer*, A.C. Gough, J.N. Primrose and C.D. Johnson
University Surgical Unit, Southampton General Hospital,
Southampton, Hampshire, U.K.

Introduction. Acute Pancreatitis (AP) is an inflammatory disorder, most commonly caused by gallstones, alcohol and drugs, although up to 30% of cases are idiopathic. Interactions between environment/diet and genotype may affect an individual's predisposition to AP via the alteration of oxygen free radical levels and/or the inappropriate metabolism of xenobiotics. In this study, we have examined four polymorphic xenobiotic metabolising enzymes, Cytochromes P450 CYP1A1, CYP2D6, CYP2E1, and N-Acetyltransferase 2 (NAT2) to assess their influence on susceptibility to AP.

Methods. Genomic DNA was extracted from 80 Caucasian AP patients and age/sex matched random unaffected controls. Polymerase Chain Reactions were performed using specific oligonucleotide primers and restriction endonucleases to detect the genetic polymorphisms within the CYP1A1, CYP2D6, CYP2E1 and NAT2 genes.

Results. From the genetic analysis, 100% (20/20) of patients with alcohol-induced AP were NAT2 slow acetylators, compared with 67.5% (54/80) in the random population (Chi-Squared Test $P < 0.01$). No statistically significant difference in slow acetylator frequency was observed in the gallstone-induced AP or idiopathic AP when compared with the random population. No association was observed between the occurrence or aetiology of AP and CYP1A1, CYP2D6 or CYP2E1 genetic polymorphisms.

Conclusions. These results suggest that the NAT2 slow acetylator status may be associated with an increased risk of alcohol-induced AP, but not gallstone or idiopathic AP. In alcohol-induced AP, induction of CYP2E1 catalysed oxidation and impaired N-Acetylation of promutagens such as nitrosamines may increase the risk of pancreatic tissue damage.

SIMULTANEOUS STUDIES OF EXOCRINE PANCREATIC FUNCTION AND ULTRASOUND DUCTOGRAPHY IN THE SECRETIN TEST.

S. Osawa, K. Kataoka, J. Sakagami, C. Kawasaki, N. Takemura, A. Nakabayashi, M. Monguchi, M. Kato, K. Kashima.
Third Department of Internal medicine, Kyoto Prefectural University of Medicine, Kyoto 602, Japan.

Introduction. The diagnosis of chronic pancreatitis (CP) usually is based on imaging studies and pancreatic function test. However, the discrepancy in the diagnosis is often seen between imaging and functional tests. In Japan, the secretin test as a duodenal intubation test is now considered the "gold-standard" test of exocrine pancreatic function. In the present study, we monitored the pancreatic duct diameter (PDD) on ultrasonography (US) and the exocrine function simultaneously after an intravenous bolus injection of secretin (100 IU). Our aims was to determine the relationship between PPD and exocrine function in the secretin test, and the clinical meaning of combining tests. **Subjects and Methods:** The secretin test with PPD measurement was examined in 70 subjects composed of 30 control subjects (C), 26 patients with probable CP (P), 14 patients with definite CP (D). The diagnosis of CP was based on the diagnostic criteria for CP by the Japan Pancreas Society in 1995. In the secretin test, we analyzed fluid volumes, bicarbonate concentrations and amylase activities of 6 aliquots of duodenal aspirate per 10 min for 60 min following an injection of secretin. Simultaneously, PPD was determined at the body of the pancreas on US 1, 2, 3, 5, 10, 15, 20, 30 and 40 min after the secretin injection. **Result:** The average of the basal PDD in C, P and D group was 1.1, 1.1 and 3.3 mm, respectively. Although PDD was increased in any group following the secretin injection, there was no difference in a time to reach the maximal dilatation of PDD among 3 groups. PDD response to secretin was expressed as a percent increase of the maximal to the basal PDD (M/B ratio). The M/B ratio in C, P and D group was $185 \pm 9\%$, $161 \pm 8\%$ and $134 \pm 8\%$, respectively. The M/B ratio in D group was significantly less than C and P group ($p < 0.005$, respectively). In comparison to the results of the secretin test, the M/B ratio significantly correlated with maximal bicarbonate concentration ($r = 0.401$, $p = 0.0005$) as well as the volume ($r = 0.361$, $p = 0.002$). **Conclusion:** It is suggested that changes in PDD on US following the secretin stimulation correspond to the degree of exocrine pancreatic impairment. Combining US ductography in the secretin test may be useful to evaluate exocrine pancreatic function.

ENDOSCOPIC SEPTOTOMY WITH PANCREATIC DRAINAGE IN CASES OF RESTENOSIS OF SURGICAL DOUBLE PAPILLOPLASTY FOR CHRONIC OBSTRUCTIVE PANCREATITIS

A. Pap, L. Bálint, A. Kovács-Megyesi, V. Balgha,
2nd Dept. Med. St. Imre Hospital, Budapest, Hungary

Surgical transduodenal papillotomy is a very effective intervention in cases of chronic obstructive pancreatitis resulting in definitive amelioration of pancreatic outflow and enzyme secretion. However, in some cases it can be complicated with a severe restenosis of the divided papilla of Vater with painful relapses of pancreatitis provoked by ductal hypertension some years after plastic surgery. In these cases endoscopic classic double repapillotomy could be dangerous because of risk of bleeding, perforation and further restenosis of the postoperative scars. In the presented three cases we found restenosis of the papilla of Vater 3-6 years after surgical double papillotomy for chronic pancreatitis. After extended endoscopic septotomy with needle-nife papillotomy between the pancreatic and biliary outlet along a 5-7 F pancreatic drain another 7-10 F drain was placed into the pancreatic duct for 2-3 months to prevent restenosis and dilate suprapapillary stricture not accessible for papillotomy. All of the three patients are doing well since removal of stents without pain, relapses and progressive dilatation of the pancreatic duct until now, however, the follow-up time is only 3-6 months.

Conclusion. Endoscopic septotomy with needle-nife papillotomy can be performed in patients with restenosis of surgical double papillotomy. Long-term stenting with double prostheses seems to be necessary to progressively dilate additional suprapapillary strictures and prevent early restenosis. Late results should be evaluated by thorough long-term follow-up with ultrasonography and functional tests.

ANTICYTOKINES MANAGEMENT ON ACUTE PANCREATITIS

A.Perejaslov.

Faculty Surgery Department, Medical University, Lviv, Ukraine

Proinflammatory cytokines, such as TNF- α , IL-6, IL-8, play an important role in the pathogenesis of acute pancreatitis. The administration of anti-inflammatory cytokines, cytokine receptor antagonists and various drugs are used for the decreasing of negative effects of cytokines or inhibition of cytokine production. With this goal three groups of remedies were used: corticosteroids, cytostatics and pentoxifylline. Forty-two patients with acute pancreatitis, which evaluate as severe (APACHE II score more than 7) were studied. The increased level of all cytokines was marked in all patients after admission. In the complex of the intensive care the hydrocortisone in doses 100 mg/day was includes in patients of the first group (n=12), the pentoxifylline in doses 200 mg/day was include in patients of the second group (n=12) and fluorouracil in doses 5 mg/day - in third group. The control group compiled 6 patients. Through day after the treatment start, the decrease of levels of all cytokines was noted in patients of first and third group. At the same time, in patients of the second group the level of TNF- α decreased and the levels of IL-6, IL-8 significantly did not change. Serum levels of TNF- α , IL-6 and IL-8 return slowly to normal values after 7 days in patients of the main groups. Infusion of hydrocortisone and pentoxifylline did not evoke the adverse reactions, infusion of fluorouracil in 4 patients accompanied by nausea, diarrhea and myocardial ischemia, what determined the necessity of the drug cancellation. The development of the systemic complications of acute pancreatitis did not observe in patients of these groups. The level of cytokines remains the high during first five days in the control group. The multiple-organ failure develops in three patients of the control group on the background of the traditional management.

Thus, the administration of corticosteroids inhibit the secretion of TNF- α , IL-6 and IL-8. The xanthine derivative pentoxifylline inhibits both the production and action of TNF- α . The including in the complex management of acute pancreatitis these remedies improve the clinical course of the disease.

DIFFERENTIATION OF CULTURED ISLETS INTO DUCTULAR AND ACINAR CELLS

PM. Pour, G Liu, B Schmied, MP Moyer.

UNMC/Eppley Cancer Center, University of Nebraska Medical Center, Omaha, NE and University of Texas, San Antonio, TX.

Introduction Maintaining islets in culture has remained a problem. This has hampered generations of islet stem cells for possible treatment of diabetes mellitus. We have been able to culture Syrian hamster islets in a defined medium indefinitely.

Material and Methods. Freshly isolated islets from Syrian hamsters were hand-picked and cultured in a M3:6 medium. After rocking for 14 days and removing fibroblasts, islets were hand-picked, placed in culture dishes, and examined at weekly intervals histologically, immunohistochemically, and electron microscopically.

Results The isolated islets showed typical structures of islets with no contamination with exocrine cells. Cultured islets floated in the medium during the first 14 days and tended to adhere to each other. After 14 days, fine ductular structures, not seen in the freshly isolated islets, appeared within all islets. At 21 days, the islet cells gradually lost their granules and were replaced by undifferentiated cells of ductular cell morphology. These ductular-like cells formed lumen and typical microvilli and were surrounded by typical islet cells intermingled with undifferentiated cells. Single or group of cells showing characteristics of acinar cells and intermediary cells of acinar-ductular, acinar- β cell, or acinar- α cell appeared between the ductular structures and endocrine cells. After 21 days, the exocrine cells disappeared and were replaced by multilayered epithelium that covered the surface of the islets. At 28 days, the epithelial cells gradually migrated into the surrounding area to form a monolayer of monomorphic undifferentiated cell population.

Conclusion Formation of ductular and acinar cells from pure islet cells indicates that under certain conditions pancreatic exocrine cells can arise from cells within islets. Whether these cells present stem cells or transdifferentiation of endocrine cells is presently unclear.

THE ROLE OF PRO- AND ANTI-INFLAMMATORY CYTOKINES IN PATHOGENESIS OF ACUTE PANCREATITIS

A.Perejaslov*, S.Chooklin.

Faculty Surgery Department, Medical University, Lviv, Ukraine

One is conception of the pathophysiology of acute pancreatitis is based on the balance between pro- and anti-inflammatory cytokines. As is known, the TNF- α , IL-6 and IL-8 play an important role in systemic inflammatory response syndrome and IL-4 and IL-10 inhibits the synthesis of cytokines by the mononuclear phagocytes. Due to this the levels of TNF- α , IL-6, IL-8, IL-4 and IL-10 were measured in 32 patients with acute pancreatitis. Venous blood was sampled on the first, third and seventh days after admission. The more significant increase of all inflammatory cytokine levels was noted in patients graded as severe (APACHE II score more than 7) compared with mild group. At the same time, the significant decline of IL-4 level and insignificant rise of IL-10 was noted. The substantial changes of IL-4 and IL-10 levels in the patient with the mild course were not marked. The developments of the systemic complications accompanied by the increase of inflammatory cytokine levels, especially of TNF- α and IL-8, with the simultaneous increase of IL-10 levels and decrease of IL-4 levels. The levels of TNF- α and IL-8 did not decrease during first four days in patients with the complicated pancreatitis, while the IL-6 levels did decrease on the third day and then increased again. The decrease of IL-4 levels in these patients was observed also. On the favourable course of acute pancreatitis the serum levels of all inflammatory cytokines slowly decreased to the normal value with the simultaneous increase of IL-4 levels.

Thus, in patients with the destructive pancreatitis the imbalance between pro- and anti-inflammatory cytokines is observed, what is necessary take into account during the conservative management.

VALUE OF INTRADUCTAL CYTOLOGY AND BIOPSY IN THE DIAGNOSIS OF PANCREATIC TUMOR

J Pozsár Zs Tóth-Baranyi, L Topa, Zs Csapó*, K Simon**, L. Flautner* Á Pap, 2nd Dept Med, Pathology**.

St. Imre Hospital, 1st Sept Surgery, Semmelweis Univ*, Budapest, Hungary

Early diagnosis of pancreatic cancer is rarely possible because of symptomless nature of the disease in early stages. Screening with ultrasonography (US) followed by computer tomography (CT) in suspicious cases is not sensitive enough and diagnostic work-out has to involve endoscopic retrograde cholangiopancreatography (ERCP) with histology or at least cytology in most cases. Percutaneous fine-needle aspiration is claimed to promote tumor-cell seeding, thus intraductal brush-cytology or biopsy should replace it if deep catheterization of pancreatic duct is possible. However, diagnostic efficacy of the intraductal approach is not known. In the last year, we performed ERCP in 52 patients with pancreatic tumor. Cytology or biopsy was taken in 29 patients (both in 10 cases with further supplementary techniques in 2 other patients). The intraductal cytology confirmed ERCP diagnosis in 11 patients, it was negative in 11 cases. The intraductal biopsy was positive in 3 and negative in 9 patients. Both techniques were successful in 3 cases, only cytology in 1 patient, neither confirmed ERCP diagnosis in 6 cases. In 5 patients duodenal biopsy also helped the work-out however, it was negative in 2 cases with highly suspicious lesions.

Conclusion Intraductal cytology and biopsy can confirm diagnosis of pancreatic cancer in 50 % and 33%, respectively but ERCP remains the gold standard until magnetic resonance imaging (MRCP) will replace it for diagnostic purposes. Operative endoscopy for intraductal sampling and palliation will keep its important role even later on.

THE EFFECT OF CIPROFLOXACIN ON PANCREATIC REGENERATION IN RATS AFTER CHRONIC ETHANOL FEEDING

G. Rydzewska*, A. Dąbrowski, G. Jurkowska, A. Gabryelewicz, Gastroenterology Dept., University Medical School, Białystok, Poland

Recently we postulated that chronic ethanol feeding can cause pancreatic injury by modulation of phospholipase D (PLD) activity (an early marker of regeneration). On the other hand quinolone antibiotic, ciprofloxacin (Cipro), which inhibit prokaryotic cell growth and protein synthesis, is known to improve the recovery from liver injury after ethanol. The present study was undertaken to determine the influence of Cipro on PLD activity and other parameters of pancreatic regeneration after chronic ethanol feeding. **Methods:** Male rats were pair fed *ad libitum* with isocaloric liquid Lieber DeCarli diet with or without ethanol content. After 6 weeks of feeding alcoholic and non-alcoholic rats received Cipro (p.o. 100mg/kg/day) or saline for 4 additional weeks. At the end of treatment some rats received also 1 h infusion of caerulein (Cae) (0.25 µg/kg/h), to stimulate PLD activity. After 6 and 10 weeks of different treatment modes, rats were killed, dispersed pancreatic acini were prepared and loaded with ³H myristic acid to label phosphatidylcholine pool, and phosphatidic acid (³H PA) was counted as a marker of PLD activity. Pancreatic weight, amylase, chymotrypsin, protein, RNA and DNA content in pancreas were measured. For *in vitro* experiment dispersed acini from healthy rats were prepared, incubated with Cipro (5 µg/ml) and PA accumulation was than measured. **Results:** 1/Body weight and pancreatic weight were comparable in all groups. 2/ PLD activity after 4 weeks of antibiotic treatment in alcoholic rats was significantly higher than in untreated alcoholic animals. 3/ Cae infusion in Cipro treated alcoholic animals cause 195% increase in PLD activity (comparable to the control), but in alcoholic rats without antibiotic, Cae was not able to stimulate PLD activity. 4/Cipro treatment caused significant increase in chymotrypsin (60%), RNA (38%) and DNA (61.3%) content in alcohol fed group; total protein and amylase content remain unchanged. 5/*In vitro* in dispersed pancreatic acini antibiotic had no effect on PA accumulation. **Summary:** Cipro significantly increased PLD activity, chymotrypsin, RNA and DNA content in pancreatic tissue in alcohol treated rats, but did not alter all these parameters in groups without ethanol. **Conclusion:** Cipro is not a trophic factor itself, but may reverse negative effects of ethanol on pancreatic regeneration, however the mechanism of this action is unclear. The observed effect of this antibiotic treatment may be of clinical relevance in the setting of alcoholic pancreatitis as quinolone are often used in the treatment of this disease.

DO THE PATIENTS WITH CONTINUOUS ABDOMINAL PAIN AND ELEVATED SERUM PANCREATIC ENZYMES REALLY HAVE CHRONIC PANCREATITIS ?

S. Saito*, K. Kita, C. Y. Morioka, K. Ohzawa, A. Watanabe
Third Department of Internal Medicine, Toyama Medical and Pharmaceutical University, Toyama, Japan

Introduction. Some patients complain of persistent abdominal pain associated with high serum levels of pancreatic enzymes, but without definite signs of chronic pancreatitis. This condition has been regarded as possible or mild variant of chronic pancreatitis. In the present report, we proposed a new pathophysiological hypothesis and therapeutic strategies for this condition. **Patients and Methods.** Six patients, 2 males and 4 females, 32 to 62 yrs old, with persistent abdominal pain (more than 3 yrs.) and elevated serum pancreatic enzyme levels have been treated in our department. US, CT and ERCP did not show any significant abnormality in any patient. One or more pancreatic enzymes, i.e., serum p-type isomylase, elastase-1 or trypsin, showed sustained elevation. Peroral trypsin inhibitors had been administered but had failed to induce a sufficient response. From precise medical interviews, a vicious psycho-somatic cycle consisted of the following three processes was hypothesized: 1) Depressive mood and anxiety inducing hypersecretion of pancreatic juice. 2) Elevation of the intraductal pressure resulting from pancreatic hypersecretion causing abdominal pain and increasing the serum levels of pancreatic enzymes. 3) Exacerbation of the symptoms aggravating the depressive mood and anxiety of the patient. Based on this hypothesis, a therapeutic strategy, focusing particularly on the physician-patient relationship was formulated. The patients were treated under this strategy and have been followed up for 2 to 8 years at the authors' clinic. **Results.** All the six cases showed rapid improvement not only in their physical symptoms but also in their quality of life within a few months after initiating treatment. Serum pancreatic enzyme levels returned to normal in 5 of 6 cases. No complication has developed during follow-up period. **Conclusions.** The pathophysiology in these patients was completely different from that of definite chronic pancreatitis, and the condition should be considered a functional digestive disorder similar to functional dyspepsia or irritable bowel syndrome.

LIVER MEDIATES THE ACTIVATION OF ALVEOLAR MACROPHAGES DURING ACUTE PANCREATITIS

L. Sabater, D. Closa, L. Fernández-Cruz*, G. Hotter, J. Roselló-Catafau.

Department of Surgery, Hospital Clinic, Barcelona, Spain
Medical Bioanalysis Department, IIBB, CSIC-Barcelona, Spain.

Introduction. The liver has been proposed as a source of mediators that influences the lung damage in acute pancreatitis. The aim of this work is focused on the activation of alveolar macrophages in a model of experimental lung damage associated with acute pancreatitis and the influence of the liver in this activation.

Methods. The study design included four groups of male Wistar rats (300 g b.w.). In the first group, pancreatitis was induced by intraductal administration of sodium taurocholate (5%). In the second group, an end-to-side portocaval shunt was performed immediately before pancreatitis induction in order to prevent the initial passage through the liver of substances released by organs involved in the inflammatory process of the pancreas. A group of animals with intraductal administration of physiologic saline and a group with portocaval shunt alone were also included as control groups in the study. Three hours after pancreatitis induction, physiologic saline administration or portocaval shunting, a bronchoalveolar lavage was performed and alveolar macrophages were obtained. Cells were counted, cultured in 6 dish plates, incubated for 1 h at 37°C under 5% CO₂ in air, and then, washed to remove nonadherent cells. Supernatants of cultured alveolar macrophages were obtained after 24 h of cell culture at 37°C under 5% CO₂ in air. Macrophage activation was evaluated by the release of NO, TNF and MIP-2. NO generation was measured by nitrite accumulation. TNF and MIP-2 were measured by using a commercial EIA kit.

Results. Induction of pancreatitis was associated with the activation of alveolar macrophages reflected in the increased generation of NO, TNF and MIP-2. All these changes were prevented when a portocaval shunt was performed before the induction of pancreatitis. Portocaval shunt had no effect in the local severity of pancreatitis, reflected by serum lipase levels.

Conclusion. This study suggest that the passage through the liver of inflammatory mediators released from the damaged pancreas mediate the activation of alveolar macrophages, which play a pivotal role in the development of lung injury associated with acute pancreatitis.

(a) K-RAS GENE MUTATION AND LOSS OF HETEROZYGOSITY AT P53 GENE LOCUS RELATIVE TO HISTOLOGICAL CHARACTERISTICS IN MUCIN-PRODUCING TUMORS OF THE PANCREAS

(b) Y. Sakai*, A. Yanagisawa, Y. Kato, H. Saisho.
(c) Department of Pathology [Y. S., A. Y., Y. K.], Cancer Institute, Tokyo; First Department of Medicine, Chiba University School of Medicine [Y. S., H. S.], Chiba, Japan.

Introduction. To clarify genetic alterations based on the histological characteristics of ductal epithelium and examine the spatial relationship of different types of genetic alterations in the early stage of pancreatic carcinogenesis, we conducted an extensive, total-area, multifocal analysis of K-ras gene mutations and loss of heterozygosity (LOH) at p53 gene locus occurring in cases of mucin-producing tumor (MPT) of the pancreas.

Patients and Methods. We studied three cases of MPT: One case each of intraductal papillary tumor (IPT), ductectatic mucinous cystic neoplasm (DMCN) and megacystic mucinous cystic neoplasm (MMCN), which were previously verified to contain various atypias of ductal epithelium including carcinoma, and to harbor K-ras gene mutation and LOH of p53 gene. After histological examination, a total of 126 sites were microdissected from the section representative of each entire lesion of the three cases, and the genetic analyses were performed.

Results. In all three cases, K-ras mutations were found in tissue with mild atypia of ductal epithelium, and always (100%) in regions of moderate atypia or higher, whereas LOH of p53 gene was seen in moderate atypia or higher, and at 50% or more in severe atypia (carcinoma). LOH of p53 gene was always associated with K-ras mutation. In contrast to K-ras mutations, LOH of p53 gene showed a more gradual tendency to increase with atypia. Moreover, in all three cases, K-ras mutation was distributed widely throughout the tumor, but LOH of p53 gene was localized to one or a few histologically homogeneous areas. While the IPT and DMCN cases showed single types of K-ras mutation and LOH of p53 gene, the MMCN case presented two types of each genetic alteration occurring separately in different areas.

Conclusion. From these data we could confirm that K-ras mutation occurs in the early stage of tumorigenesis, and LOH of p53 gene superimposes on the K-ras mutation during the course of tumor progression. In addition, these alterations were homogeneous within the individual area of the same histological characteristic. Further, in the MMCN case the double mutations of K-ras gene may indicate a different histogenesis of this type from the other two types of MPT, a notion that has long been proposed from a clinical and anatomical view point.

A BILE ACID PANCREATITIS MODEL IN MICE

Y. Sakai, K. Takeda, M. Sunamura, M. Kobari, S. Matsuno.

First Department of Surgery, Tohoku University School of Medicine, Sendai, Japan.

Introduction. There was no suitable severe acute pancreatitis model in mice. We produced desoxycholate-induced acute pancreatitis in mice and determined cytokines in serum and abdominal lavaged samples.

Materials and Method. 60 ICR mice (male, 30-40gBW) were divided into 2 groups. Group 1 received only sham operation (laparotomy). Group 2 had desoxycholate-induced acute pancreatitis. The necrotizing pancreatitis was induced by retrograde injection of 15 μ l of 5% sodium desoxycholate into common biliopancreatic duct. 1. Survival rates were observed up to 72-hour after the induction. 2. Blood samples were taken at 1-, 12-, and 24-hour after the induction. Moreover lavaged samples were taken at same time. Pancreas was removed and examined histologically. Serum amylase was determined. TNF- α and IL-10 in serum and lavaged samples were determined by ELISA.

Results. 1. Survival rates were at 72-h were 100% (15/15) in group 1, and 67% (10/15) in group 2. 2. Highly significant increases of serum amylase were found in group 2 compared with group 1. TNF levels in lavaged samples in group 2 is significantly higher than in group 1 only at 1-h, serum TNF levels remained unchanged. IL-10 levels in lavaged samples were significantly higher than in group 1, and gradually increased up to 24-h, serum IL-10 levels in group 2 were also significantly higher than in group 1 at 24-h.

Conclusion. We produced bile acid pancreatitis model in mice. It showed hyperamylasemia and necrotizing pancreatitis. Increased TNF levels in lavaged samples and increased IL-10 levels in serum and lavaged samples were demonstrated. The model could provide opportunity to evaluate therapy.

EVALUATION OF PRE- AND INTRA-OPERATIVE ASVS (ARTERIAL STIMULATION AND VENOUS SAMPLING) FOR DIAGNOSIS AND SURGICAL RESECTION OF INSULINOMA

M. Sakon, T. Aoki, H. Ohzato, S. Kishimoto, S. Ohshima, T. Yamada, S. Nakamori, K. Dohno, K. Umeshita, M. Gotoh, O. Ishikawa, S. Imaoka, Y. Hasuiki, K. Shibata, M. Monden.

Department of Surgery II, Osaka University Medical School, Department of Surgery, The Center of Adult Disease, Department of Surgery, National Osaka Hospital, and Department of Surgery, Ikeda Municipal Hospital, Osaka, Japan.

Introduction. Precise tumor localization is essential for surgical treatment of insulinoma. In addition to various imaging modalities, ASVS (arterial stimulation and venous sampling) is also used to localize insulinoma. However, the role of ASVS in the diagnosis and the surgical treatment of insulinoma remains to be elucidated.

Patients and methods. Pre- and intraoperative ASVS were performed in six patients with insulinoma together with imaging including ultrasonography, CT scan, and angiography. Preoperative ASVS was performed by withdrawal of blood from the right hepatic vein 0, 30, 60, 90, 120 seconds after a bolus injection of calcium gluconate (0.025mEq/kg) into proper hepatic artery, gastroduodenal artery, splenic artery, and superior mesenteric artery. For intraoperative ASVS, the arterial catheter was introduced into the feeding artery. ASVS was performed before and after surgical resection. Immunoreactive insulin (IRI) concentrations and the IRI ratio (IRI concentration at each time interval after calcium injection / baseline IRI concentration) were determined by the conventional or quick IRI method. **Results.** By preoperative ASVS, the site of the tumor was identified in all six patients, but only in four patients by imaging. The IRI ratio varied widely from 3.6 to 99.2, but a cut-off value of 3.0 clearly differentiated between feeding and non-feeding arteries. Intraoperative ASVS using the feeding artery showed a similar elevation of IRI levels, but disappeared after tumor resection in all but one patient. In two patients, resection of the tumor was confirmed during surgery by intraoperative measurement of IRI levels. **Conclusions.** A combination of ASVS and conventional imaging modalities is useful for determination of the precise site of insulinoma. Resection of the tumor could be confirmed intraoperatively by ASVS.

DEVELOPMENT OF REGIONAL STOP-FLOW CHEMOTHERAPY FOR NON-RESECTABLE PANCREATIC DUCTAL CARCINOMA: A PRELIMINARY REPORT

M. Sakon, S. Ohshima, H. Ohzato, S. Nakamori, T. Aoki, N. Higaki, T. Yamada, H. Nagano, K. Dohno, K. Umeshita, M. Gotoh, M. Monden. Department of Surgery II, Osaka University Medical School, Suita, Osaka, JAPAN.

INTRODUCTION. Prognosis of non-resectable pancreatic ductal carcinoma is still poor in spite of the use of various therapeutic modalities. Stop flow chemotherapy with aortic clamping was recently developed, but complications like gastroduodenal ulcer may develop. We studied the effect of regional stop-flow chemotherapy which allows a specific infusion of the anti-cancer drug into the pancreas.

Patients and methods. Eight consecutive patients with non-resectable pancreatic ductal carcinoma were treated by regional stop-flow chemotherapy. After laparotomy, the celiac artery, superior mesenteric artery, right and left gastric arteries, and splenic artery were clamped. A cocktail of MMC (10-30mg), CDDP (20-40mg), and 5-FU (250-500mg) in 300 ml of saline was infused through the catheter introduced into the common hepatic artery, followed by vascular clamping for 20-30min. The tissue blood flow was measured by laser Doppler flowmetry to evaluate the degree of ischemia. Arterial infusion chemotherapy (CDDP 10-20mg and 5-FU 250-500mg) was performed through this catheter every two weeks thereafter.

Results. Pancreatic tissue blood flow markedly decreased after regional vascular clamping. Although chemotherapy did not reduce the size of the tumor in every patient, the growth of the main tumor was arrested for 2 to 6 months in all patients. The level of CA19-9 decreased or did not change for 2 to 8 months except in two patients who also had liver metastasis. In patients without liver metastasis, the prognosis was better compared with the historical control subjects, but in those with liver metastasis, it was still poor and died within 8 months. Anorexia and vomiting were noted in all patients, but were well controlled by conventional therapies.

Conclusion. Regional stop flow chemotherapy is effective in patients with non-resectable pancreatic carcinoma. However, for the better prognosis, it is important to control liver metastasis.

ACUTE EXPERIMENTAL PANCREATITIS IS AMELIORATED BY THE DEACTIVATION OF PLATELET ACTIVATION FACTOR (PAF).

A. Saluja, B. Hofbauer, M. Bhatia, J.L. Frossard, L. Bhagat, H.S. Lee, and M. Steer. Harvard Medical School and Beth Israel Deaconess Medical Center, Boston, USA.

The severity of acute pancreatitis varies over a wide range, but the determinants of severity are unknown. Recently, PAF has been implicated in several inflammatory conditions including pancreatitis. We report on the effects on pancreatitis of deactivating PAF by the recombinant enzyme PAF-acetyl hydrolase (rPAF-AH) (ICOS Corporation, Bothell, WA).

Methods: Caerulein (i.v., 10 μ g/kg/hr for 5 hr) was used to induce mild edematous interstitial pancreatitis in rats, while biliopancreatic duct ligation under sterile conditions was used to induce severe necrotizing pancreatitis in opossums.

Results: Rats receiving rPAF-AH (5 mg/kg) 30 minutes before the start of the caerulein infusion showed a modest reduction in hyperamylasemia, vacuolization of acinar cells and pancreatic inflammation at a histological level, but not in pancreatic edema. In opossums, the rPAF-AH given 1 to 4 days after duct ligation resulted in significant amelioration of acinar cell injury and necrosis as determined by morphometric analysis of hematoxylin-eosin-stained sections.

Conclusion: The effect of PAF in regulating the progression of pancreatic injury, though not edema, is significant in mild secretagogue-induced pancreatitis, while it plays a pivotal role in the progression of pancreatic injury resulting from biliopancreatic duct ligation. These observations suggest that rPAF-AH may have significant benefits even if administered after the onset of pancreatitis.

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PROTECTION AGAINST PANCREATITIS-INDUCED LUNG INJURY IN OPOSSUMS BY RECOMBINANT PLATELET-ACTIVATING FACTOR ACETYL HYDROLASE (rPAF-AH). A. Saluja, B. Hofbauer, M. Bhata, H S. Lee, L. Bhagat, J.L. Frossard, and M. Steer. Harvard Medical School and Beth Israel Deaconess Medical Center, Boston, USA.

Acute lung injury, whose most frequent clinical manifestation is adult respiratory distress syndrome, is a frequent accompaniment of severe acute pancreatitis. The injury-causing mechanism is not well understood. However, platelet-activating factor (PAF), which is generated during the onset of acute pancreatitis, has recently been implicated in several inflammatory conditions including pancreatitis. This study uses the enzyme rPAF-AH (ICOS Corp., Bothell WA) to deactivate PAF and details the effects of this drug on the severity of lung injury.

Methods: The biliopancreatic duct of opossums was ligated under sterile conditions, leading to the development of severe necrotizing pancreatitis within 24 hours, with increasing severity over several days. Increased serum amylase and lipase, necrosis of pancreatic acinar cells, and infiltration of inflammatory cells characterized the disease. One to four days after duct blockage, opossums were administered either rPAF-AH or a placebo.

Results: The placebo-treated animals showed acute lung injury three days post-ligation. The severity of injury progressed with time and was marked by enhanced microvascular permeability as quantitated by extravasation of FITC-labeled albumin into the lungs and morphological damage seen in hematoxylin-eosin-stained paraffin sections. Remarkably, animals treated with rPAF-AH were completely free of pancreatitis-induced lung injury.

Conclusion: The present observations show that (i) acute lung injury is a sequel of pancreatitis caused by biliopancreatic duct ligation in opossums, (ii) suggest that PAF plays a critical role in inducing pancreatitis-related lung injury, and (iii) demonstrate that rPAF-AH prevents such injury in opossums, leading to the possibility that it will be of therapeutic value in preventing lung injury in patients of pancreatitis administered after the onset of pancreatitis [Supported by a research grant from the ICOS Corporation]

PROGRESSIVE DECREASE OF PANCREATIC EXOCRINE SECRETORY RESPONSE TO CCK IN WBN/KOB RATS

K. Sasaki, S. Taguchi¹⁾, I. Arai²⁾, S. Amagaya, Y. Komatsu³⁾, K. Mitamura¹⁾, G. M. Green³⁾

¹⁾ 2nd Dept. Int. Medicine, School of Medicine, Showa Univ., Tokyo, Jpn., ²⁾ Tsumura Kampo & Pharmacog. Labs., Ibaraki, Jpn., ³⁾ Dept. Physiology, Univ. Tex. Health Sci. Ctr., San Antonio, TX, USA.

Introduction. WBN/Kob rat (Kob) is a diabetic and chronic pancreatitis model derived from Wistar rat and has fibrosis of the pancreas. In this study, we compared the exocrine secretion and histological changes of pancreas of Kob with that of Wistar rats. To clarify the mechanism of the pancreatic disorder, the binding of CCK-8 to the pancreatic membranes were also examined.

Methods. Male Kob and Wistar rats at 10, 12, 16 and 20 weeks were used. Cannulas were inserted into biliary and pancreatic ducts, and duodenum. Bile and pancreatic juice were returned to the duodenum continuously, and on the 3rd day, CCK-8 (250 ng/kg/hr, i.v.) was administered. Pancreatic juice was collected every 30 min in conscious rats. To measure the CCK-8 binding to pancreatic membrane, pancreatic membrane fractions were incubated with ¹²⁵I-CCK-8 for 60 min and the radioactivity of membranes were counted. The number and affinity of CCK receptors were estimated by Scatchard analysis. For histological examination, slices of pancreas were dyed with hematoxylin-eosin and azan-mallory methods.

Results. Compared to Wistar rats, the stimulation of protein output of Kob by CCK-8 was weaker from 16 weeks and continued to diminish up to 20 weeks. The bindings of CCK-8 to pancreatic membranes in Kob were lower from 12 weeks and continued to diminish up to 20 weeks. In Scatchard analysis, the insufficiency of CCK-8 binding to pancreatic membranes was derived from decreased numbers of CCK receptors. In histological examination of pancreas in Kob, proliferation of fibrous tissue and infiltration of neutrophils appeared at 12 weeks and progressively increased up to 20 weeks.

Conclusion. In Kob, histological changes in pancreas appeared and were associated with the reduction of pancreatic exocrine reaction to CCK-8. The secretory insufficiency was derived from the decrease of CCK receptor numbers in pancreatic membranes.

A CASE OF INFLAMMATORY PANCREATIC MASS

M. Sasagawa, K. Hirano, H. Nakatsuka, M. Fujita, T. Wanifuchi, I. Sato. Gastroenterology Department of Surgery, Nanbu General Hospital, Muramatsu Town, Japan

Introduction. The differential diagnosis between pancreatic cancer and inflammatory mass of the pancreas is very difficult. As the management and prognosis of these two disease is different, the selection of appropriate operation is necessary to prevent unnecessary resection. We now report on a case of inflammatory pancreatic mass diagnosed before the operation and performed segmental pancreatectomy.

Patient and method. A 73-year-old male, who had been a heavy drinker admitted to our hospital on December 5, 1997. A low density mass lesion, which occupied in the body of the pancreas, was found in CT. Then we performed MRI, Angiography, EUS to examine the mass.

Result. CT and MRI showed round mass in the pancreatic body, which was 1.2cm or 1.5cm in diameter. ERP showed smooth stenosis of the pancreatic duct in the body. Angiography, EUS, US could not detect abnormal pancreatic mass. We diagnosed the round mass as inflammatory pancreatic mass before the operation. US performed at the operation, also showed low echoic mass in the body of the pancreas, but we could not detect the mass macroscopically. According to the frozen section, the mass was diagnosed as acute inflammatory mass, then we performed segmental pancreatectomy. After operation, we got pancreatic juice 60-180ml/day through pancreatic tube from the pancreatic tail. **Conclusion.** Stenosis of the pancreatic duct may cause chronic pancreatitis in the distal side of the pancreas. Segmental pancreatectomy for the pancreatic inflammatory mass in the body is useful to keep the function of the pancreatic tail. Therefore pre-operative and intra-operative differential diagnosis is very important for the operation of inflammatory pancreatic mass.

THE REGENERATION AFTER DEVELOPMENT OF ETHIONINE-INDUCED ACUTE PANCREATITIS IN OLETF RATS

T. Sato, J. Nukawa*, A. Ikegami, A. Takahashi, H. Yoshida, S. Tanaka, K. Mitamura. Second Dept. Int. Med., Showa Univ., Tokyo, Japan

Introduction. An inbred strain of diabetic Otsuka Long-Evans Tokushima Fatty (OLETF) rats developed for study of non-insulin-dependent diabetes mellitus has been reported to be no or reduced expression of cholecystokinin (CCK)-A receptor gene in the pancreas. CCK is a crucial gastrointestinal hormone having trophic effects on pancreatic growth and regeneration. CCK is presumably involved in deterioration of pancreatitis because of supramaximal stimulation of intracellular mediators which causes disorder of enzyme secretion. We studied the effects of CCK on ethionine-induced acute pancreatitis during the earlier and later periods using OLETF rats. **Method.** Male OLETF rats (7 weeks old) and male Long-Evans Tokushima Otsuka (LETO) rats as the control group were fed by special diet containing a small amount of protein (low protein diet) for 11 days and received a daily intraperitoneal administration of 20mg/100g body weight of DL-ethionine for the last 4 days, and then they were fed by standard diet. They were sacrificed on 1, 4 and 7 days after the last injection of ethionine followed by blood collection and removal of pancreas. Pancreatic protein and DNA were measured by Lowry's and Burton's methods, respectively. Plasma CCK levels were measured by radioimmunoassay using anti-CCK-8-specific antiserum (OAL-656). **Result.** One day after development of ethionine-induced acute pancreatitis, infiltration of inflammatory cells and necrosis of acinar cells were observed in LETO and OLETF rats. The impairment of pancreas in LETO rats was more marked than that in OLETF rats during the earlier period. Mitotic indices were 0.226 ± 0.088 % in LETO rats and 0.090 ± 0.044 % in OLETF rats on day 7. Body weights decreased during ingestion of low protein diet and increased during standard diet. The maximal reduction of pancreatic protein content (PP) per DNA content (PP/DNA) in OLETF rats was observed later than that in LETO rats. After 4 days, there were no significant changes in reduction of pancreatic weight (PW) and DNA content in OLETF rats. PP/DNA, PP and PW in LETO rats were significantly higher than those in OLETF rats on day 4 and 7. Thus, the restoration of impaired pancreas in OLETF rats was delayed compared to that in LETO rats indicating that the endogenous CCK is crucial during the later period in acute pancreatitis. Plasma CCK levels on day 4 were 10.8 ± 1.5 pg/ml in LETO rats and 37.6 ± 11.8 pg/ml in OLETF rats. **Conclusion.** We developed acute pancreatitis with ethionine using OLETF rats without CCK-A receptor gene expression. The impairment of pancreas in OLETF rats was less than that in LETO rats during the earlier period. This study suggests that CCK plays an important role on the regeneration after development of pancreatitis.

CLINICAL MANAGEMENT OF PANCREATIC CYSTS DETECTED BY SCREENING ULTRASONOGRAPHY

T. Sato^{1)*}, M. A. Fujino, A. Morozumi, K. Hosoda, F. Kitahara, K. Kubo, Y. Kojima, T. Nakamura, M. Ikeda²⁾, K. Kobayashi³⁾, Y. Matsumoto⁴⁾

1) First Department of Medicine, Yamanashi Medical University, Yamanashi, 2) Department of Gastroenterology, Osaka National Hospital, Osaka, 3) Health Care Center, Yamanashi Koseiren, Yamanashi, 4) First Department of Surgery, Yamanashi Medical University, Yamanashi, Japan

Introduction. Cystic lesions of the pancreas are frequently detected by screening ultrasonography, but most of these lesions are asymptomatic and their clinical management has not been determined.

Patients and Method. In 221,310 participants of an ultrasonographic mass survey, 385 patients with pancreatic cysts were included to the epidemiological and morphological studies.

Results. The prevalence of pancreatic cyst was 0.17% (male 0.11% vs. female 0.22%, $p < 0.01$) and was significantly higher in older people than in younger people. The size of the cyst was less than 2cm in 94%. Further examination was performed in 188 patients, and we found 26 neoplastic cysts, 2 retention cysts and 5 pseudocysts. In the remaining 155 cysts we were unable to disclose their etiology. Nine of the neoplastic cysts were resected, and histological diagnosis was made (mucinous cystadenoma 3, serous cystadenoma 3, solid and cystic tumor 2 and mucinous cystadenocarcinoma 1). All of these neoplastic cysts show the findings of mural nodule and/or septal structure and/or MPD dilatation. Ultrasonographic follow-up of the pancreatic cysts over 3 years was performed in 34 cases. Eleven of the cysts were enlarged in size during the follow-up period, but 4 cysts were reduced and remaining 19 cysts were unchanged in size. The initial size of the cyst in unchanged cases (average 10.6, range 5-20mm) was significantly smaller than in enlarged cases ($p < 0.05$). The incidence of MPD dilatation and the septal structure of the cyst was significantly higher in enlarged cases ($p < 0.05$, $p < 0.01$, respectively).

Conclusion. Most of the small pancreatic cysts without a septum, a mural nodule or MPD dilatation are non-progressive. It will not be necessary to follow-up the patients so frequently.

INTRAVENOUS L-ARGININE EXCESS INDUCES NON-PARALLEL PANCREATIC SECRETION IN THE ANAESTHETIZED RAT

R.E. Schwab, J. Pozsár, E. Szepesváry, T. Gonda, Zs. Rausch, J. Hamvas, T. Miguel*, Á. Pap,

2nd Dept. Med. St. Imre Hospital, Natl. Inst. Oncology*, Budapest

INTRODUCTION. Experimental pancreatitis induced by L-arginine is an established model of metabolic pancreatitis, however, its pathomechanism is still unclear. There are observations on its effect inducing hyperstimulation possibly involving CCK and hyperstimulation of the pancreas is a recognized factor in the etiology of acute pancreatitis. **AIMS.** Investigation of the stimulatory effect of L-arginine on the pancreas in the anesthetized rat. **METHODS.** 2 groups of Wistar rats, 4 animals in each, weighing 350-400g were anesthetized with 1,6g/100g bw of urethane. The main hepatic duct was ligated after cannulation of the common pancreato-biliary duct, and the femoral vein. I.v. infusion of normal saline was started and fractions of pancreatic secretion were collected hourly for 8 hours. In the experimental group 500mg/100g bw of L-Arginine was given after 2 hours of control period for another 2 hours with a 4 hour follow up afterwards. Controls received normal saline only. Specific activity and enzyme ratios were calculated following measurements of amylase, lipase, trypsin activity and total protein content. **RESULTS.** There was a sevenfold increase in trypsin secretion peaking after 3 hours, a gradual, fivefold increase in its specific activity after 4 hours, with a fivefold increase in the trypsin-to-amylase ratio, after 3 hours from the beginning of the L-Arginine infusion. No change was seen in controls. **CONCLUSIONS.** Intravenous L-Arginine excess induces a stimulatory effect of non-parallel nature on the rat pancreas, resembling that of CCK. These results correspond well with previous data showing a loss of trypsin content in the pancreas after administration of L-Arginine.

DISTRIBUTION OF TGF β 1 AND ITS RECEPTORS SUGGESTS DIFFERENT STROMAL REACTIONS BETWEEN PANCREATIC DUCT CELL CARCINOMA AND CHRONIC PANCREATITIS.

K. Satoh, T. Shimosegawa, M. Koizumi and T. Toyota.

The Third Department of Internal Medicine, Tohoku University School of Medicine, Sendai, Japan.

Introduction. Within recent years evidence has been produced establishing the relationship of cancer cells and stromal cells for tumor invasion. One mediator which may play an important role in such processes is transforming growth factor β 1 (TGF β 1), because this multifunctional cytokine regulates cellular functions such as epithelial cell growth, differentiation and the synthesis of extracellular matrices. Although it is well known that TGF β transduces the signaling through a heterodimeric complex of the type I and type II TGF β receptors (T β RI and T β RII), no study has been carried out to examine their expression simultaneously in tissues of pancreatic duct cell carcinoma (PDC). In addition, because the interstitial fibrosis seen in chronic pancreatitis (CP) resembles the desmoplasia of PDC, comparison of their expression between the tissues of PDC and CP would be interesting.

Patients and Method. We investigated the expression of TGF β 1 and its receptors, T β RI and T β RII in surgically resected tissues of 21 PDC and 13 CP by immunohistochemistry using specific antibodies.

Results. In the epithelial cells of PDC and CP, no significant differences was found in the expression of TGF β 1, T β RI and T β RII. In contrast, there was a tendency that stromal expression of this cytokine and its receptors, especially that of T β RII, were stronger in PDC than in CP.

Conclusion. Our data suggest that stronger stromal expression of TGF β 1 and its receptors may contribute to the essential difference in the pathobiology of desmoplasia associated with PDC and the interstitial fibrosis of CP.

PANCREATIC TUMOR: COMPARISON OF MR PANCREATOGRAPHY AND ENDOSCOPIC RETROGRADE PANCREATOGRAPHY

J. H. Seo*, J. H. Lee, M.-J. Kim*, J. B. Chung, Y. M. Moon, J. K. Kang, I. S. Park.

Gastroenterology Department, Diagnostic Radiology Department* and Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Korea

Introduction. Magnetic resonance pancreatography (MRP) is a noninvasive imaging technique for the visualization of the pancreatic duct system similar to those obtained with endoscopic retrograde pancreatography (ERP). The aim of this study was to determine the role of MRP versus ERP in the diagnosis of pancreatic tumors.

Patients and Method. Sixteen patients (10 male and 6 female, mean age 61 years) with pancreatic tumors underwent MRP and ERP between March 1997 and December 1997. MRP was performed with single shot fast spin echo sequence on a 1.5T system. All images were retrospectively reviewed by a radiologist and a gastroenterologist in conference. Both MRP and ERP were compared for visualization of the head, body, and tail portion of the pancreatic duct separately and scored as excellent (4), good (3), fair (2), poor (1), and no visualization (0). The overall diagnostic confidence of both modalities also was graded subjectively from non-diagnostic image (0) to definite information (4). The final diagnoses derived from surgical findings (n=9) or imaging findings and clinical follow-up (n=7) were as follows: pancreatic cancer (n=8), mucin-producing pancreatic cancer (n=2), mucinous ductectatic tumor (n=4), serous cystadenoma (n=2). Paired t-test was done to assess the statistical significance of the difference between the MRP and ERP images.

Results. Mean scores of visualization of the pancreatic duct by MRP and ERP were 2.88 and 3.44 in the pancreatic head ($p=NS$), 3.06 and 2.19 in the pancreatic body ($p=NS$), and 3.06 and 1.38 in the pancreatic tail ($p < 0.01$). Mean score of the diagnostic confidence was 3.94 in MRP and 2.31 in ERP, which had a statistically significant difference ($P < 0.05$). In 8 patients with obstruction of pancreatic duct due to malignant lesions, MRP demonstrated both the proximal and distal site of obstruction in the pancreatic duct while ERP only visualized the distal site of obstruction. MRP was superior in defining the extent of tumor because of the visualization of the surrounding pancreatic parenchyma and the relationship of the ducts. In two cases of serous cystadenoma with lack of communication between the pancreatic duct and cystic neoplasm, MRP characterized the lesion precisely whereas ERP showed no information.

Conclusion. MRP is better than ERP in visualization of the pancreatic duct proximal to the site of obstruction and assessment of the extent of tumor in the diagnosis of pancreatic neoplasm. MRP is also beneficial compared to ERP in the diagnosis of cystic neoplasm without communication with pancreatic duct.

DIFFERENTIAL DIAGNOSIS OF PANCREATIC CANCER FROM CHRONIC PANCREATITIS USING *IN VIVO* ³¹P MAGNETIC RESONANCE SPECTROSCOPY

D.W. Seo*, J.-H. Lee, K.H. Yoon, M.G. Lee, K.-H. Lim, S.K. Lee, M.H. Kim, D.-J. Suh, Y.I. Min Department of Internal Medicine, Radiology, Asan Medical Center, Asan Institute for Life Science, Seoul, Korea

Introduction. The differential diagnosis of pancreas cancer and mass-forming chronic focal pancreatitis is quite troublesome. Recently, ³¹P magnetic resonance (MR) spectroscopy has been applied to various malignancies and phosphomonoester (PME) signal was suggested to be a marker of cell proliferation. This study was undertaken to evaluate the usefulness of ³¹P MR spectroscopy in the differential diagnosis of pancreatic cancer and chronic pancreatitis. **Methods.** Five patients with histologically proven pancreatic adenocarcinoma and five patients with chronic pancreatitis were included. All MR imaging and localized *in vivo* ³¹P MR spectroscopy of the pancreas were performed on a 1.5T system (Magnetom Vision, Erlangen, Germany) with two-dimensional chemical shift imaging technique (TR/TE 32/3 msec, slice thickness 40mm, total acquisition time 17min). Peak areas of PME, phosphodiester (PDE), inorganic phosphate (Pi) and α , β and γ -ATP were determined and relative ratios of PME/ β -ATP and PDE/ β -ATP were calculated. **Results.** Spectroscopic metabolite changes were summarized below.

	Chronic Pancreatitis	Pancreas Cancer	p value
PME	0.38±0.24	66.25±16.34	<0.01
PDE	71.65±13.79	46.63±18.35	>0.05
Pi	11.01±3.71	24.43±19.72	>0.05
PME/ β -ATP	0.05±0.05	3.96±1.04	<0.01
PDE/ β -ATP	5.38±0.84	2.59±1.10	>0.05

The levels of PME and PME/ β -ATP were significantly higher in patients with pancreatic cancer than those with chronic pancreatitis. However, the levels of PDE, PDE/ β -ATP and Pi were not significantly different between two groups. **Conclusions.** ³¹P MR spectroscopy may be a useful tool in the differential diagnosis of pancreatic cancer and chronic pancreatitis and the increased signal of PME seems to be associated with the rapid proliferation of cancer cell.

TUBULAR COMPLEXES IN THE HUMAN PANCREAS

M. Shimizu*, M. Hirokawa, T. Manabe.

Department of Pathology, Kawasaki Medical School, Kurashiki, Japan

Introduction. Tubular complexes have been noted in experiments on animals, such as the rat, dog, and rabbit, but in humans, they have been only described as a rare finding of pancreatitis, especially in the postacute phase. Recently, we encountered a case with tubular complexes without any history of pancreatitis, and herein describe the case with a review of the literature.

Case Report. The patient was a 76-year-old man who had undergone a right middle lobectomy for lung cancer (adenocarcinoma). After operation, he was treated with chemotherapy because of metastasis. He entered the hospital with a chief complaint of cough and general fatigue. His condition deteriorated and he died of respiratory failure two months later. An autopsy revealed pleural and pericardial carcinomatosis with metastases to the liver, right adrenal gland, diaphragm, esophagus, vertebrae and lymph nodes. The cause of death was considered to be respiratory failure. As an incidental finding, the head of the pancreas showed a lesion of ductule-like structures measuring 2.5 mm. This lesion was surrounded by fibrous connective tissue. Immunohistochemically, the ductule-like structure was positive for keratin and epithelial membrane antigen (EMA), and focal positivity was noted for alpha-1-antitrypsin and alpha-amylase. It was negative for carcinoembryonic antigen (CEA), CA19-9, chromogranin A, neuron specific enolase (NSE), insulin, glucagon, somatostatin, and pancreatic polypeptide. Based on these findings, we diagnosed this lesion as tubular complexes.

Discussion. In general, tubular complexes are thought to be the result of regressive degeneration of acinar cells followed by pancreatic injury. However, we could not find any history of pancreatitis or histological evidence of pancreatic injury in this case. In addition, tubular complexes in the pancreas show similar microscopic findings to those of von Meyenburg complexes in the liver. Therefore, the possibility of tubular complexes of hamartomatous nature in the human pancreas can not be ruled out completely.

PANCREATIC DUCTAL ABNORMALITIES IN PATIENT WITH CHOLEDOCHAL CYST

S.S.Sharma* and M.Bhojak

Department of Gastroenterology, SMS Medical College Hospital, Jaipur, India

Introduction: There are limited reports of pancreatic ductal abnormalities in patients with choledochal cyst. 8.1% patients in one series were reported to have pancreatic ductal abnormalities. Dilated ducts, ductal calculi and anomalous pancreatobiliary ductal union were anomalies reported.

Methods: Pancreatic ductal abnormalities in 40 consecutive patients of choledochal cyst diagnosed on ERCP were studied by two independent observers. In 31 patients pancreatic duct could be clearly visualized in its entire length. Diameters of duct in head, body, tail and branch to uncinate process were measured and correction for magnification was done. Abnormalities of side branches were also noted if there was filling of side branches. Length & diameter of common channel were also measured if common channel was clearly visualized.

Results: Mean age of patients with pancreatic ductal abnormalities was 24 years. Pancreatic ductal abnormalities were seen in 8 patients (25.8%). The abnormalities detected were dilated pancreatic duct (8), stones in pancreatic duct (2), dilated branch to uncinate process (4), stricture of pancreatic duct (1). Dilated side branches were seen in 3 patients. Anomalous pancreatobiliary ductal union was seen in 2 patients. In one patient there was pancreas divisum. The mean diameter of pancreatic duct in head, body & tail in patients with dilated pancreatic duct were 6.0, 8.4, 5.0 mm respectively while mean diameter of pancreatic duct in 25 normal healthy persons of same age group were 3.2, 2.8, 1.7 mm respectively (P<0.01, 0.005, 0.01 respectively).

Conclusion: Abnormalities of pancreatic duct on ERCP were seen in 25.8% of patients of choledochal cyst suggesting that choledochal cyst in this group represent an anomaly of entire pancreatobiliary system rather than of biliary tract alone or choledochal cyst in some way induces changes in pancreatic duct.

METASTATIC PANCREATIC CANCER: CLINICOPATHOLOGICAL STUDY OF AUTOPSY CASES

M. Shimizu*, E. Nakamura, T. Manabe.

Department of Pathology, Kawasaki Medical School, Kurashiki, Japan

Introduction. Although the incidence of pancreatic cancer has been increasing, there have been only a few papers dealing with metastatic pancreatic cancer and little is known about its clinicopathological features.

Patients and Method. We reviewed 1,171 autopsies performed at Kawasaki Medical School from 1988 to 1994, and found 467 cases of malignant tumor excluding cases of primary pancreatic cancer. We investigated the presence or absence of pancreatic metastasis in these cases, and analyzed the age, sex, primary site, gross findings, and microscopic findings in cases with pancreatic metastasis.

Results. We found 71 cases with pancreatic metastasis (15%) among the 467 cases of malignant tumor investigated. They included 43 males and 28 females who ranged in age from 2 to 85 years. These cases consisted of 53 primary epithelial tumors and 18 non-epithelial tumors. The former cases included adenocarcinoma (31 cases), undifferentiated carcinoma, and squamous cell carcinoma, while the latter included leukemia (5 cases), malignant lymphoma, leiomyosarcoma, multiple myeloma, and malignant melanoma. As a primary site, the stomach was the most common site (13 cases, 18%), followed by the lung (12 cases), liver, extrahepatic bile duct, breast, gallbladder, urinary bladder and ovary in order. Grossly, metastasis was not identified in 23 cases (32%). As for the pattern of tumor spread, most cases were considered to have been due to lymphatic and/or vascular spread, while some cases seem to have been due to direct tumor invasion. In about two-thirds of these cases, the distribution of tumor cells microscopically had an inter- and intralobular pattern.

Conclusion. As a primary site of metastatic pancreatic tumor, the stomach, liver, and biliary tract were the most common. Interestingly, undifferentiated carcinoma was often found in cases of bile duct or urinary bladder cancer with pancreatic metastasis. Acute pancreatitis associated with pancreatic metastasis was also observed in some cases.

CHRONIC INFLAMMATORY PANCREATITIS

M. Shimizu*, S. Iwamoto, T. Manabe, T. Tsunoda.

Departments of Pathology and Gastroenterological Surgery, Kawasaki Medical School, Kurashiki, Japan

Introduction. According to the revised Marseille-Rome classification of pancreatitis (1988), chronic inflammatory pancreatitis (CIP) is recognized as an entity distinct from other forms (calcifying, obstructive, or autoimmune) of chronic pancreatitis. However, the pathology of CIP has not been fully described.

Patients and Method. We reviewed pancreatotomy specimens from five patients with chronic inflammatory pancreatitis. Resected specimens were histologically and immunohistochemically examined in detail.

Results. The patients ranged in age from 51 to 68 years and all were men. Two cases showed tumor-forming pancreatitis clinically and the others showed diffuse enlargement of pancreas. Pancreatic carcinoma was suspected preoperatively in most of these cases. Four out of five cases presented with jaundice and one case had elevated serum CA19-9 and DUPAN-2 levels. Microscopically, lymphoid follicles were observed and lymphocytic infiltration was marked. Exocrine parenchyma of the pancreas was replaced by fibrosis, and perineural lymphocytic infiltration was also noted. Tortuous ducts were often seen.

Immunohistochemically, lymphocytes were predominantly T lymphocytes (UCHL-1 positive). Alpha-smooth muscle actin and vimentin were positive in the interlobules. One case revealed focal destruction of the duct epithelium by inflammation, a finding similar to that in recently described "chronic duct obstructive pancreatitis (CDOP)".

Discussion. All patients were males, and lobular as well as periductal infiltrates consisted of mainly T lymphocytes. Tortuous ducts as well as perineural lymphocytic infiltration were observed in most cases. There may be some overlap between CIP and CDOP, since no history of alcohol was obtained in our series. Further investigation is necessary.

PERIACINAR FIBROBLAST-LIKE CELL ISOLATED FROM HUMAN PANCREATIC ACINI AND ITS POSSIBLE ROLE IN PANCREATIC FIBROSIS

Y. Shintani, T. Saotome*, F. Nakamura, J. Tamba, U. Yoshioka, H. Inoue, Y. Fujiyama and T. Bamba

2nd Dept. of Internal Medicine, Institute of Molecular Neurobiology*, Shiga University of Medical Science, Shiga, Japan

Pancreatic mesenchymal cells existing in periacinar region are thought to be involved in intralobular fibrosis and acinar cell function. In the present study, we successfully isolated and cultured PFC derived from human pancreas. Further, we have shown the characteristics of human PFC morphologically and immunocytochemically. Human PFC was isolated from pancreatic acini of normal pancreatic tissue, which was resected in the mass by the operation of non-pancreatic disease. Briefly, the acini were obtained by means of digesting specimens of pancreatic tissue with Dispase, type IV collagenase and DNase. Pancreatic acini were cultured with DMEM containing 20%FBS at 37°C in 5%CO₂. On day 1 after seeding of the isolated pancreatic acini, small numbers of spindle-shaped cells (i.e. PFC) appeared adjacent to the acini, and several days after, migrating spindle-shaped cells predominated. In electron microscopic observation, it revealed a number of microfilaments, which frequently forming dense bodies in human PFC. Using the human PFC at passage 3, immunocytochemical staining for type I and III collagen/procollagen, fibronectin, prolyl hydroxylase β subunit, type IV collagen, laminin, α -smooth muscle actin, vimentin and non-muscle myosin were performed. Immunoreactivities were observed in all staining. Further, augmentation of the expression of α -smooth muscle actin by TGF- β 1 was confirmed in the Western blot analysis. De novo collagen synthesis in human PFC was examined. It was stimulated by TGF- β 1 in a dose-dependent manner (0.01-1.0 ng/ml), but not by PDGF. The proliferation of human PFC was also examined. PDGF (0.1-1.0 ng/ml), but not TGF- β 1 induced a dose-dependent increase in cell proliferation. Taken together, the present study revealed that human PFC derived from human pancreatic acini has a myofibroblast-like phenotype following stimulation with TGF- β 1 and that cell proliferation and collagen synthesis in human PFC were affected by cytokines. These findings suggest that PFC has a crucial role in the regulation of periacinar fibrosis in chronic pancreatitis, whereby PFC is excessively activated by cytokines such as TGF- β 1 and PDGF.

PANCREATIC BILE DUCT OBSTRUCTION DETERIORATES CAERULEIN-INDUCED ACUTE PANCREATITIS IN RATS

M. Shunkai*, Y. Takeyama, M. Adachi, T. Ueda, Y. Hori, K. Takase, M. Yamamoto, Y. Kuroda.

First Department of Surgery, Kobe University School of Medicine, Kobe, Japan

Introduction. Biliary pancreatitis, which usually remains edematous, sometimes progresses to hemorrhagic. We hypothesized that pancreatic duct obstruction deteriorates pancreatitis, and investigated the effects of pancreatic bile duct ligation (PBDL) on rat caerulein-induced pancreatitis.

Methods. In vivo: Pancreatic bile duct ligation (PBDL) was performed in combination with 6-h intravenous continuous caerulein infusion on Male Wistar rats. Serum amylase level and pancreatic histology were evaluated. In vitro: Isolated pancreatic acini were collected from the rats with 3-h PBDL, and amylase and LDH release induced by various concentration of cholecystokinin octapeptide (CCK8) were estimated.

Results. In vivo: Serum amylase level was significantly elevated and hemorrhagic change in the pancreas occurred in the rats with PBDL 1 h before caerulein administration. On the other hand, the rats in which PBDL was added 2h after the beginning of caerulein administration, the hemorrhagic change was not observed. In vitro: Preceded PBDL reduced amylase secretion from the acini induced by maximal (100pM) or supramaximal (10nM) dose of CCK8 to 50% of control. Although no significant effect of PBDL was observed on the basal LDH release, preceded PBDL significantly enhanced LDH release in the presence of supramaximal dose of CCK8.

Conclusion. Preceded pancreatic duct obstruction deteriorates pancreatic histology of edematous pancreatitis to hemorrhagic via enhancement of intracellular autolysis.

THE DYNAMICS OF INTERSTITIAL CHEMICAL MEDIATORS IN THE EARLY STAGES OF PANCREATIC FIBROSIS

M. Shiozaki*, Y. Takeda, K. Katsu

1 Second Department of Internal Medicine, Osaka Medical College, Takatsuki, Japan 2 Department of Gastroenterology, Ijinkai Takeda General Hospital, Kyoto, Japan

Introduction: The role of the different chemical mediators in the early stages of pancreatic fibrosis occurring as a result of acinar cell damage is still unclear. The aim of the present study was to investigate the dynamics of various chemical mediators in the early stages of chronic pancreatitis using an experimental model. **Methods:** A mixed (ZO) solution of the simple protein zein and the cytotoxic oleic acid was prepared. A volume of 100 μ l of the ZO solution was infused from the end of the common bile duct of rats and the pancreas was resected 3 or 24 hours, or 2, 4 or 7 days later. A part of the resected pancreas was immunohistologically stained with HE and the myofibroblast marker α -smooth muscle actin (α -SMA). The resected pancreas was homogenized and lipoperoxide, leucotriene B₄, CINC/GRO-1 equivalent to rat IL-8, and TGF- β 1 (ELISA) concentrations in the supernatant were measured and converted to content per pancreatic wet weight.

Results: ① *Changes in the pancreatic histology.* Edematous pancreatitis was observed 1 day after infusion. After 2 days, marked mononuclear infiltration of the interlobular interstitium was evident, and fibroblasts were seen. After 4 days, there was further destruction of the lobular structure and fibroblast hyperplasia was observed. After 7 days, destruction of the lobular structure was marked, and early signs of fibrosis were seen inside the lobules. ② *Changes in the interstitial fibroblasts.* The spindle-shaped fibroblasts that appeared after 2 days were negative for α -SMA. After 4 days, a perithelium-like aggregation of interstitial cells strongly positive for α -SMA was seen adjacent to the area around the peripheral pancreatic duct bifurcation. These were myofibroblasts derived from activated fibroblasts. The α -SMA stainability of the interstitial cells decreased after 7 days. ③ *Changes in the interstitial chemical mediators.* (1) Lipoperoxide content reached a peak after 24 hours and gradually declined thereafter. (2) Leucotriene B₄ content increased after 3 hours and quickly decreased thereafter. (3) Rat IL-8 (CINC/GRO) content rose for 2 days and then fell. (4) TGF- β 1 content increased for 4 days, at which time it peaked, and then fell slightly after 7 days. **Conclusions:** Pancreatic fibrosis appears to begin with acinar cell damage as a result of free-radical-mediated reaction, as reflected by a rise in lipoperoxide content. Next, the mediators leucotriene B₄ and IL-8 responsible for inflammatory cell infiltration were induced. This was followed by induction of TGF- β 1, which plays an important role in the early stages of pancreatic fibrosis; that is, in the fibroblast hyperplasia and the transformation of fibroblasts to myofibroblasts.

T CELL RESPONSE DIRECTED AGAINST MUTATED K-ras PEPTIDES IN PANCREATIC CANCER PATIENTS.

Yoshiharu Shono, Hiroshi Tanimura, Hiroki Yamaue, Makoto Iwahashi, Takuya Tsunoda, Masaji Tani, Shizuma Mizobata, Mikihiro Nakamori, Hajime Tanaka and Kenji Matsuda.
Second Department of Surgery, Wakayama Medical School, Wakayama 640, Japan.

Introduction. Mutations in codon 12 K-ras are frequently found in pancreatic cancer. It has been demonstrated that human T cells have the potential to recognize tumor cells expressing mutated ras peptides. However, it remains unclear whether T cells can recognize the same mutated peptides which express in the own tumor cells.

Material and Method. We typed pancreatic cancer tumor for the mutations of K-ras oncogene by mutant allele specific amplification (MASA) method, and the sensitivity of MASA method was confirmed by direct sequencing method. Next, T cell response was analyzed against 18-mer peptides (encompassing residues p4-21 of p21 ras, YKLVVVGAXGVGKSAIT where X is Gly, Val, Cys, Asp) deduced from codon 12 sequence of K-ras oncogene in peripheral blood lymphocytes originated from 4 patients with pancreatic cancer.

Results. Two patients had T cell response against 18-mer peptide with mutated peptide Val, whereas one patient had the mutation of Asp from Gly, and another patient had no mutation. However, no T cell response has been recognized in healthy volunteers. Moreover, there was no identity between the mutation of K-ras peptides and T cell response in pancreatic cancer patients.

Conclusion. Thus, it is suggested that the Val-peptide can induce the T cell response in pancreatic cancer patients, and these T cells might lyse the tumor cell clones possessing the mutated K-ras peptides carcinogenesis and cancer progression.

BIOACTIVITY AND TRYPSIN-SENSITIVITY OF LUMINAL CHOLECYSTOKININ RELEASING FACTOR (LCRF) PEPTIDES.

A. W. Spannagel, J. Knudsen, R. A. Liddle, G. H. Greeley, Jr., D. Guan, J. R. Reeve, Jr. and G. M. Green*

Dept. Physiol., Univ. TX. Hlth. Sci. Ctr., San Antonio, USA; Dept. Surg., Univ. TX. Med. Br., Galveston, USA. Inst. of Biochem., Odense Univ., Odense, DK, Dept. of Med., Duke Univ. Med. Ctr., Durham, NC, USA; Dept. of Med., CURE/VA/UCLA Dig. Dis. Ctr., Los Angeles, CA, USA.

Introduction. LCRF, an 8 kd peptide isolated from rat intestinal secretion [PNAS 93: 4415-20, 1996] is a putative intraluminal regulator of CCK. We compared bioactivity of synthetic LCRF peptides to responses obtained with other potential regulators of intestinal hormone secretion, monitor peptide (MP), diazepam binding inhibitor (DBI) and GRP, and determined the trypsin-sensitivity of synthetic LCRF₁₋₃₅.

Methods. LCRF₁₋₆, LCRF₁₁₋₂₅, and LCRF₁₋₃₅ were synthesized. DBI₁₋₈₆ (porcine native and rat recombinant) and MP (recombinant) peptides were tested. GRP₁₋₂₇ and DBI₃₃₋₅₀ were obtained commercially. Conscious rats prepared with pancreatic, biliary, intra-duodenal (i.d.), and i.v. cannulas were used. **1st study:** during i.d. infusion of 10% of the secreted pancreatic juice, LCRF₁₋₃₅ was infused continuously i.d. and plasma CCK and pancreatic exocrine secretion were monitored. **2nd study:** CCK releasing activity of bolus i. d. injections of various peptides was tested using a sensitive in vivo rat bioassay. Both i.d. and i.v. routes of administration were tested. Doses ranged from 10 ng to 10 µg. Direct effects of LCRF₁₋₃₅ on the pancreas were tested using isolated pancreatic acini.

Results. **1st study:** LCRF₁₋₃₅ significantly increased plasma CCK and pancreatic enzyme secretion by 97% and 188%, respectively, and i.v. LCRF₁₋₃₅ significantly stimulated pancreatic secretion and CCK release. MK-329 eliminated the pancreatic secretory responses. **2nd study:** LCRF₁₁₋₂₅, LCRF₁₋₃₅, purified native LCRF, and MP were bioactive, but LCRF₁₋₆, GRP₁₋₂₇, DBI₁₋₈₆, DBI₃₃₋₅₀, and trypsin-treated LCRF₁₋₃₅ were not. LCRF₁₋₃₅ did not stimulate isolated pancreatic acini. All active peptides produced bell-shaped dose-response curves.

Conclusions. DBI does not regulate CCK secretion in conscious rats. Synthetic 35-AA and 15-AA LCRF peptides containing Lys at position 19 are bioactive. Cleavage of LCRF₁₋₃₅ at Lys-19 inactivates the peptide.

ROLE OF LUMINAL CCK RELEASING FACTOR (LCRF) AND GRP IN PANCREATIC RESPONSE TO BILE-PANCREATIC JUICE DIVERSION (BPJD).

A. W. Spannagel, G. H. Greeley, Jr., R. A. Liddle, G. M. Green*,
Dept. Physiol. and Cell Biol., Univ. TX. Hlth. Sci. Ctr., San Antonio, TX; Dept. Surgery, Univ. TX. Med. Branch, Galveston, TX; Dept. of Med., Duke Univ. Med. Ctr., Durham, NC.

Introduction. The objective of this study was to examine the role of luminal CCK releasing factor (LCRF) and gastrin releasing peptide (GRP) in mediating the pancreatic exocrine- and CCK secretory-response to BPJD.

Methods. Rats were prepared with biliary, pancreatic, intestinal, and intravenous cannulas. Pancreatic protein and fluid secretion were monitored before and after BPJD. Rats were given i.v. either normal rabbit serum (A), LCRF antiserum (B), GRP antiserum (C), or both LCRF and GRP antiserum (D) before BPJD.

Results. *denotes significantly different from group A. Basal protein secretion (mg/kg/30 min) was 17±2 (A), 16±2 (B), 13±3 (C), and 14±2 (D). Basal fluid secretion (µL/kg/30 min) was 493±58 (A), 438±51 (B), 288±46* (C), and 297±46* (D). Incremental protein output (Δ mg/kg/30 min) during BPJ diversion was 31±2 (A), 20±3* (B), 12±4* (C), and 15±2* (D). Incremental fluid output (Δ µL/kg/30 min) during BPJ diversion was 444±47 (A), 252±52* (B), 164±81* (C), and 204±49* (D). Plasma CCK (pM) during BPJ diversion was 21.9±2.3 (A), 9.0±2.6* (B), 9.5±2.4* (C), 7.2±1.4* (D). Inhibiting endogenous GRP prevented any significant increase in pancreatic exocrine secretion during BPJ diversion. Inhibiting endogenous LCRF significantly reduced, but did not prevent, the increases in pancreatic exocrine secretion seen during BPJ diversion.

Conclusions. CCK stimulation of pancreatic exocrine secretion during BPJ diversion requires the presence of GRP. Optimal CCK secretion during BPJ diversion is dependent on LCRF, GRP, and other regulatory factors.

DIFFERENT COMPOSITION OF HUMAN AND ANIMAL PANCREAS, DOES IT MATTER FOR PANCREATIC DISEASE?

B. Sternby*, A. Vihert,
Department of Medicine, University Hospital, Lund, Sweden*,
Department of Pathology, Moscow, Russia.

Introduction. In addition to slightly different anatomy, the lipid contents of human and rat pancreas differ, but are more similar than those of ox and guinea-pig pancreas (Durand et al. *Pancreas*, 1987; 326-332). It is well known that the same experimental disease model gives different results in different animals.

Materials and Methods. Pancreatic glands from 25 alcoholics, 86 patients with heart disease, and 1618 rats, and pancreatic powders from horse and pig were examined for amylase, β-hexose amidase, carboxyl ester lipase, colipase, elastase, insulin, lipase, phospholipase A₂, PSTI, trypsin, A₂₈₀, Lowry, and pH. Pancreatic glands were minced, delipidated, and air-dried. Pancreatic powder was dissolved in buffer (1 g/10 ml, pH 5.0 and 8.0), stirred at room temperature for 30 minutes and centrifuged 2x10 minutes (cell centrifuge, 2000 rpm). The supernatant was used for the above mentioned examinations.

Results. A pronounced variation in the composition of the different pancreas was found. Even some differences in the two human groups were seen, which support findings that eg. obese patients, who get pancreatitis, are in a more serious condition than lean patients.

Conclusions. The differences in compositions of pancreatic enzymes, hormones, other proteins, and lipids may explain why good animal models have solved only few of the questions in the understanding of the causes of human pancreatic diseases, and have contributed very little to treatment and prevention.

PANCREATIC SUPPLEMENTS REDUCE THE SYMPTOMATIC RESPONSE OF HEALTHY SUBJECTS TO A HIGH FAT MEAL. F. L. Suarez, M.D. Levitt, J. Adsheed, Minneapolis V.A. Med. Ctr., U of MN, Minneapolis, MN, J.S. Barkin* U of Miami/Mt. Sinai Med. Ctr., Miami, Florida

Healthy subjects commonly experience fullness, bloating and mild abdominal discomfort following ingestion of large meals. When frequent and severe, these symptoms commonly are attributed to the irritable bowel syndrome. While more rapid digestion presumably would reduce these symptoms, unimpressive results have been obtained in previous studies employing pancreatic supplements that are denatured in the stomach and thus provide minimal enhancement of digestive activity. The purpose of the present study was to determine if microencapsulated pancreatic enzymes (MPE) (Creon[®]; Solvay Pharm. Inc) reduce the severity of postprandial symptoms experienced by healthy volunteers after ingestion of a high fat meal. **METHODS:** In a randomized, double-blind, crossover study, 18 subjects ingested a breakfast consisting of 185 g of cookies (1196 calories and 72 g of fat) and three MPE capsules or identical placebo. The severity of gastrointestinal symptoms and frequency of flatus passages were recorded for 17 hours, and end-alveolar breath samples were obtained hourly for 10 hours. **RESULTS:** For the entire test period, ingestion of pancreatic supplements was associated with a significant ($P<0.05$) reduction in bloating, and reductions in perception of gas, flatus frequency, and nausea that had P values between 0.05 and 0.10. Independent analysis of early versus late symptomatology showed that MPE produced significant ($P<0.05$) reductions in bloating, gas, and fullness during the dinner to bedtime period. MPE had no significant effect on breath H_2 or CH_4 excretion. **CONCLUSIONS:** MPE reduces postprandial symptoms in healthy subjects. These "normal" postprandial symptoms form a continuum with the complaints observed in irritable bowel or non-ulcer dyspepsia. The possibility that these common conditions also might benefit from treatment with pancreatic supplements needs to be reinvestigated utilizing microencapsulated pancreatic enzyme preparations that deliver active enzyme to the duodenum *pari passu* with the meal.

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TNF- α -INDUCED APOPTOSIS IN A PANCREATIC CANCER CELL LINE BY INHIBITION OF NF- κ B

M. Suganuma^{1,2}, S. Kajino¹, T. Tetsuka¹, T. Kawabe¹, Y. Marugami², T. Funabiki², T. Okamoto¹

¹Dept. of Molecular Genetics Nagoya City University, Nagoya, Japan.

²Dept. of Surgery, Fujita Health University, Toyoake, Japan.

Introduction. The transcription factor NF- κ B is protective against apoptotic killing induced by TNF- α . We investigated, whether the NF- κ B is protective against apoptosis by TNF- α using the human pancreatic cancer cell line MIA PaCa-2, which is relatively resistant killing by TNF- α . To potentially block the activation of the NF- κ B in response to TNF- α , we transfected I κ B gene, which is inhibitor NF- κ B. **Methods** Apoptosis was evaluated by propidium iodide staining and the appearance of sub-G1 population by the cytofluorometric analysis and the Hoechst 33258 staining with the microscopic observation. The cellular localization of NF- κ B was determined by immunostaining using antibody against the p65 subunit of NF- κ B. Transient luciferase assay was carried out to evaluate the effects of I κ B gene transfer in blocking NF- κ B actions. To directly evaluate the roles of NF- κ B in blocking apoptosis, MIA PaCa-2 were transfected with p65 and/or I κ B genes in combination with a plasmid expressing GFP (green fluorescent protein) and the gene-transduced cells were visualized by GFP expression. **Results** 1) TNF- α induced apoptosis in the MIA PaCa-2 cells in a dose dependent manner. 2) Pre-treatment with IL-1 β , known to activate NF- κ B, attenuated TNF- α induced apoptosis (TNF- α , 34.5% vs. IL-1 β + TNF- α , 15.4%). 3) When those cells were transfected with a plasmid expressing p65 they became resistant to the TNF- α induced apoptosis. 4) In the co-transfection experiments with p65 and I κ B genes, the extent of apoptotic response increased. **Conclusion** 1) NF- κ B was effective in blocking TNF- α induced apoptosis response in the MIA PaCa-2. 2) The I κ B gene transfer increased the sensitivity to the apoptosis. These data suggested that, if tumor cell sensitivity to TNF- α controlled by NF- κ B by the gene transfer of I κ B may result in a dramatic enhancement of killing over TNF- α alone.

HISTOPATHOLOGICAL STUDY ON SO-CALLED TUMOR-FORMING TYPE OF CHRONIC PANCREATITIS

K. Suda*, M. Takase.

Department of Pathology, Juntendo, University School of Medicine, Tokyo, Japan

Introduction. Morphologically, chronic pancreatitis is characterized by irregular sclerosis with destruction and loss of the exocrine parenchyma. It is known that at some stage during disease process chronic pancreatitis clinically presents tumorous swelling, often suspected to be carcinoma. This stage is also known as the tumor-forming stage of chronic pancreatitis.

Patients and Method. Ten cases of so-called tumor-forming type of chronic pancreatitis which were detected as a tumor on computed tomographic scanning or physical examination were studied histopathologically. Eight of the 10 cases were in heavily alcoholic drinkers. In 7 cases the tumorous lesion was located in the head of the pancreas, and in 3 cases in the body and tail. In all of the former 7 cases there was obstructive jaundice due to stenosis of the intrapancreatic common bile duct.

Results. Macroscopic examinations revealed tumorous swelling or sclerotic appearance in the pancreatic tissue. Histologically these lesions showed tumorous swelling with (N=8) or without (N=2) a background of chronic pancreatitis. In the former, the tumorous swelling consisted of extensive fibrosis including necrosis or abscess and stone, and there was successive transition to the surrounding chronic pancreatitis pattern. The other 2 tumorous lesions presented inter- and intraobular fibrosis with lymphoid hyperplasia and were adjacent to normal pancreatic tissue.

Conclusion. So-called tumor-forming type of chronic pancreatitis shows at least two distinct types: reparative tumorous swelling within a background of chronic pancreatitis, which is considered to have given rise to the tumor at some stage, and lymphoid and fibrous proliferation in normal pancreatic tissue, which is considered to represent an autoimmune-related disease process.

OPERATIVE PROCEDURES ON PERIPYLORIC VESSELS IN PYLORUS-PRESERVING PANCREATODUODENECTOMY (PPPD) —EFFECTS ON GASTRODUODENAL BLOOD FLOW

S. Sumi, S. Iwasaki, M. Koike, H. Watanabe, G. Xu, T. Urushihata.

Y. Inoue, M. Teramoto, M. Itakura, S. Yano, Y. Nio, K. Tamura.

First Department of Surgery, Shimane Medical University, IZUMO, JAPAN.

Introduction. In PPPD for advanced diseases, peripyloric lymph nodes are resected sacrificing the first gastric branches of the right gastric artery (RGA) and right gastroepiploic artery (RGEA). We examined the effect of different procedures of peripyloric vessels on gastroduodenal blood flow. **Patients and Methods.** In 14 PPPD cases (8 pancreatic cancer, 3 biliary cancer and 3 other diseases) operated in our Department from February 1995 to May 1997, gastroduodenal tissue blood flow was measured intraoperatively by a laser flow meter (MBF3D, Moor Instruments, U.K.). Measurement was performed three times [before starting resection, after removal of the organs (REM) and after finishing reconstruction (REC)] at the serosal surface of the duodenum (2cm anal from the pyloric ring), antrum (2 cm oral from the pyloric ring) and body of the stomach, respectively. Change was estimated as a percent of the value obtained before resection. **Results.** In 13 cases, one of the following modes was performed: type 1 (n=5): preservation of RGA and cutting RGEA near its origin, type 2 (n=5): cutting both RGA and RGEA near their origins with all gastric branches preserved, Type 3 (n=3): resection of the first gastric branches of both RGA and RGEA. In one case excluded from this study, RGA was cut at the origin and the first gastric branch of RGEA was resected. In general, blood flow significantly decreased after the removal of the organ (REM) in the duodenum and the antrum, then recovered to some extent after reconstruction (REC) in the duodenum. No significant change was observed in the body. The table shows the results.

Table. Values: mean $\pm$ SE (%). * $p<0.05$ vs type 1.

Type	Duodenum(REM/REC)	Antrum(REM/REC)	Body(REM/REC)
1	56 $\pm$ 12 / 66 $\pm$ 9	76 $\pm$ 9 / 59 $\pm$ 9	86 $\pm$ 15 / 84 $\pm$ 14
2	33 $\pm$ 5 / 55 $\pm$ 11	78 $\pm$ 20 / 55 $\pm$ 8	80 $\pm$ 15 / 73 $\pm$ 28
3	11 $\pm$ 3* / 16 $\pm$ 1*	34 $\pm$ 4 / 36 $\pm$ 11	93 $\pm$ 14 / 104 $\pm$ 27

Conclusion. RGA can be cut without significant decrease in blood flow. Sacrificing the first branches of both RGA and RGEA significantly decreases duodenal blood flow, which limits the length of duodenum to be preserved.

OPERATIVE PROCEDURES ON PERIPYLORIC VESSELS IN PYLORUS-PRESERVING PANCREATODUODENECTOMY (PPPD) —EFFECTS ON POSTOPERATIVE COURSE

S. Sumi, H. Watanabe, G. Xu, T. Urushihata, S. Iwasaki, M. Koike, Y. Inoue, M. Teramoto, M. Itakura, S. Yano, Y. Nio, K. Tamura.

First Department of Surgery, Shimane Medical University, IZUMO, JAPAN.

Introduction. PPPD has a clinical merit over classical Whipple procedure in which distal stomach is resected. Recently, we have expanded the indication of PPPD to the majority of pancreatic cancer cases unless the stomach and proximal duodenum is involved. In some of these cases, peripyloric lymph nodes were resected sacrificing the first gastric branches of the right gastric and right gastroepiploic vessels. We tried to evaluate the clinical significance of this procedure. **Patients and Methods.** In 50 PPPD cases (pancreatic cancer (PC): 20, biliary cancer (BC): 17, other diseases (OD): 13) treated in our Department from May 1991 to November 1996, operative procedure and postoperative course was reviewed. **Results.** Operative mortality was 0%. In 45 cases (90%), one of the following 3 modes was performed; type 1 (n=21): preservation of right gastric artery (RGA) and cutting right gastroepiploic artery (RGEA) near its origin, type 2 (n=12): cutting both RGA and RGEA near their origins with all gastric branches preserved, Type 3 (n=12): resection of the first gastric branches of both RGA and RGEA. In this, about 2 cm length of the proximal duodenum was preserved for anastomosis. Type 1 was used for 4 PC, 6 BC and 11 OD (7 benign, 2 potentially malignant and 2 malignant diseases). Type 2 was for 7 PC and 5 BD. Type 3 was used for generally advanced diseases of 5 PC, 5 BC and 2 OD. Operation time (OT), blood loss (BL), incidence of any kind of anastomosis-related problem (AP) and postoperative days of gastric drainage (GD), fasting (F) and hospitalization (H) is shown in the table below. (Value is mean $\pm$ SE. Cases of AP were excluded in GD, F and H. *: $p < 0.05$ vs type 1.)

Type	OT(min)	BL(gram)	AP(%)	GD(day)	F(day)	H(day)
1	440 $\pm$ 20	1230 $\pm$ 160	8/21(38)	17 $\pm$ 1.6	25 $\pm$ 1.8	62 $\pm$ 2.4
2	453 $\pm$ 30	1340 $\pm$ 300	1/12(8)	20 $\pm$ 1.8	28 $\pm$ 2.2	65 $\pm$ 6.1
3	539 $\pm$ 31*	1970 $\pm$ 400	2/12(17)	25 $\pm$ 2.8*	30 $\pm$ 2.3	70 $\pm$ 5.7

Conclusion. Type 3 was associated with major surgical stress and needed longer GD but did not increase the risk of AP. Type 3 is a possible procedure, although the more preserving mode results in the sooner recovery.

HORMONAL REGULATION OF GASTRIC EMPTYING IN CANINE EXOCRINE PANCREATIC INSUFFICIENCY

A. Suzuki, M.G. Sarr, E.P. DiMaggio*

Gastroenterology Research Unit, Mayo Clinic, Rochester, MN, USA

Background. We reported that in untreated canine pancreatic insufficiency (CPI) nutrient composition of diets altered gastric emptying (GE), increased dietary protein slows gastric emptying, and the amount of protein delivered to the duodenum directly correlates with protein intake.

Aims: To determine in untreated CPI if GE of liquids is related to plasma peptide YY (PYY) and/or neurotensin (NT) and if nutrients in duodenum or ileum are related to plasma PYY and NT. **Methods:** We prepared 3 dogs by ligating the major and minor pancreatic ducts and inserting duodenal and ileal cannulas to infuse nonabsorbable markers and to aspirate intestinal samples. Each dog was fed 1 of 5 isocaloric test meals containing 850 kcal of various nutrient composition according to a mixture design and unlabeled PEG as a liquid meal marker. Intestinal samples were aspirated every 15 min to measure nutrients (carbohydrate, fat and protein) and meal (PEG) and infused markers. After calculating luminal flow rates, GE of liquids (area under curve of the amount remaining in the stomach) and the amount of nutrients delivered to the duodenum and ileum were calculated over 6 hr. Blood samples were also obtained at 0, 15, 30, 45, 60, 90, 120, 150 and 300 min to measure plasma NT and PYY (mean postprandial concentration for 6 hr). Repeated measures ANOVA and multiple regression analysis were performed to assess differences among test meals and the relations among intestinal nutrient delivery, GE and postprandial plasma concentrations of NT and PYY. **Results:** GE of liquids correlated significantly with postprandial mean concentrations of NT ($r^2 = 0.652$, $p = 0.01$); slower GE was associated significantly with higher plasma concentrations of NT. The mean plasma concentration of PYY and NT correlated directly with duodenal delivery of protein and inversely with ileal delivery of CHO ($r^2 = 0.718$, $p = 0.02$, $r^2 = 0.694$, $p = 0.033$ and $r^2 = -0.843$, $p = 0.001$, $r^2 = -0.633$, $p = 0.011$, respectively). The mean concentration of NT correlated inversely with duodenal delivery of CHO ($p = 0.025$, $r^2 = -0.635$).

Conclusions: In untreated CPI, slower GE of liquids is related significantly to high plasma concentrations of NT. Mean concentrations of NT and PYY increase in association with duodenal delivery of large amounts of protein and delivery of small amounts of CHO to the ileum.

Conjecture: GE in untreated pancreatic insufficiency may be regulated by a protein mediated release of NT or PYY.

HEMODYNAMIC STUDIES OF ORTHOTOPIC SEGMENTAL PANCREAS TRANSPLANTATION INTERPOSING THE SPLENIC VESSELS IN DOGS

Y Suzuki*, Y Tanioka, I Matsumoto, T Deai, Y Ku, Y Kuroda

First Department of Surgery, Kobe University School of Medicine, Kobe, Japan

Introduction. There is a need to establish a live donor program of segmental pancreas transplantation because of cadaver donor shortage. We recently developed an orthotopic segmental pancreas transplant (OSPT) technique. This study was done to determine if interposing the graft splenic vessels in this technique restores physiological graft hemodynamics and reduces thrombosis rate.

Methods. This study was designed as a comparative study between OSPT with (the interposition group, $n = 11$) and without (the control group, $n = 11$) interposition of the splenic vessels. On day 7 posttransplant, the recipient dogs were relaparotomized and grafts were assessed macroscopically, microscopically and functionally. In a subset in the interposition group ($n = 6$), splenic artery and vein flows and graft tissue blood flow were monitored through the revascularization procedures.

Results. Thrombosis incidence was 9.1% and 54.5% in the interposition group and the control group, respectively ($p < 0.05$). The splenic artery and vein flows decreased markedly from 52.1 ± 17.2 mL/min and 40.2 ± 14.3 mL/min at laparotomy, to 3.0 ± 1.9 mL/min and 1.8 ± 2.0 mL/min after proximally established reperfusion, respectively. They increased significantly immediately after the interposition to 35.4 ± 7.5 mL/min and 31.5 ± 18.5 mL/min, respectively. The flows further increased to greater than 90% of the basal flows 2 hours after the interposition. In contrast, the graft tissue blood flows were not affected significantly by the interposition.

Conclusion. The interposition of the splenic vessels in OSPT decreases the thrombosis risk by producing physiological splenic flows without an adverse effect on graft tissue perfusion. OSPT with the splenic vessel interposition may be clinically applicable.

THE EFFECT OF METHYLPREDONISOLONE ON THE DEVELOPMENT OF ACUTE PANCREATITIS INDUCED BY CLOSED DUODENAL LOOP IN RATS

K. Takaoka, K. Kataoka, H. Yasuda, J. Sakagami, N. Takemura, A. Nakabayashi, M. Kato, K. Kashima.

Third Department of Internal Medicine, Kyoto Prefectural University of Medicine, Kyoto 602, Japan.

Introduction. Severe acute pancreatitis (AP) frequently leads to shock or multiple organ failure (MOF) that are responsible for a high mortality. It is known that corticosteroid inhibits a release of cytokines, an activation of leukocytes and phospholipase A_2 that may be involved in the development to severe AP. In clinical practice, a large dose of methylprednisolone (MP) is useful to treat patients with shock or MOF. However, this therapy is not common in the treatment of AP. In the present study, we determined the effect of MP in the development of AP induced by closed duodenal loop (CDL) in rats. **Materials and Methods.** Male Wistar rats, weighing 160–220g, were used in this experiment. Four cm of CDL was prepared by ligating the duodenum at two points on both sides of the bile-pancreatic duct. The rats were divided into three groups as follows; (1) sham-operation (S), (2) CDL-pancreatitis, (3) CDL-pancreatitis with MP (CDL+MP). MP (30 mg/kg body weight) was given to rats by an intravenous injection via tail vein. The laparotomy was done again 6hrs after the preparation of CDL, and the ascites was collected for measurement of the volume, trypsinogen activation peptide (TAP), IL-6 and TNF- α (ELISA). Then, blood flows of the pancreas (splenic lobe) and the left kidney were determined using a Laser Doppler blood flowmeter. Serum amylase activity, TAP, IL-6, TNF- α and hematocrit were also measured. The pancreas were removed for measurement of its wet weight and for histological evaluation of the gland. **Results.** The administration of a large dose of MP significantly decreased the pancreatic weight, hematocrit, serum amylase activity, volume and TAP concentration of ascites that increased in CDL group. Furthermore, both pancreatic and renal blood flows in CDL+MP group were significantly higher than CDL group. MP also improved the degree of pancreatic edema and necrosis induced by CDL. **Conclusion.** The present results suggest that a large dose of MP prevents the development of experimental AP in rats. MP may be useful to treat patients with severe AP.

APOPTOTIC CELL DEATH OF RENAL TUBULES IN EXPERIMENTAL SEVERE ACUTE PANCREATITIS

K. Takase*, Y. Takeyama, J. Nishikawa, M. Shinkai, T. Ueda, Y. Hori, M. Yamamoto, Y. Kuroda
First Department of Surgery, Kobe University School of Medicine, Kobe, Japan

Introduction. Mechanism for renal failure in acute pancreatitis remains unclear. We hypothesized that renal cell injury via apoptosis is involved in renal failure with acute pancreatitis.

Methods. Necrotizing pancreatitis was induced on male Wistar rats by retrograde injection of sodium deoxycholate into pancreatic duct. Six h later, the kidney was harvested and apoptosis was evaluated by in situ nick-end labeling and by DNA agarose gel electrophoresis. The ascitic fluid, which was collected 6 h after development of pancreatitis, was injected intraperitoneally into normal rats, and apoptosis in the kidney was also evaluated as described above. In vitro, apoptosis-inducing ability of the ascitic fluid was estimated using isolated rat renal tubules and normal rat kidney cell line (NRK52E) by nuclear staining and by cell cycle analysis in addition to DNA electrophoresis.

Results. Apoptosis was detected by in situ nick-end labeling on the renal tubules 6 h after induction of DCA pancreatitis in vivo, and was confirmed by DNA fragmentation. Similar tubular apoptosis was also detected 6 h after intraperitoneal injection of the ascitic fluid in normal rats. In in vitro analyses, the ascitic fluid induced nuclear and DNA fragmentations on the isolated renal tubules, and increased the apoptotic cell ratio on NRK52E cells in a time-dependent manner.

Conclusions. Apoptotic cell death of renal tubules occurs in severe acute pancreatitis, and is possibly involved in the mechanism of renal failure via apoptosis-inducing activity in pancreatitis-associated ascitic fluid.

THYMIC ATROPHY DUE TO THYMOCYTE APOPTOSIS IN EXPERIMENTAL SEVERE ACUTE PANCREATITIS

Y. Takeyama*, J. Nishikawa, T. Ueda, Y. Hori, K. Takase, M. Shinkai, M. Yamamoto, Y. Kuroda
First Department of Surgery, Kobe University School of Medicine, Kobe, Japan

Introduction. Although reduction of peripheral lymphocytes has been reported in clinical cases of acute pancreatitis, thymic change in acute pancreatitis is still unknown. To investigate impairment of cellular immunity in acute pancreatitis, alterations of thymus in the rats with acute pancreatitis were examined experimentally.

Methods. Male Wistar rats were used and two groups with pancreatitis of different grades of severity and control group for each other were developed. Edematous pancreatitis was induced by 4-h continuous intravenous administration of cerulein (5µg/kg/h), and necrotizing pancreatitis was induced by retrograde injection of 0.1 ml of 10% sodium deoxycholate into biliary-pancreatic duct. The thymus weight and number of thymocytes were estimated. Apoptosis in thymus was examined by the in situ nick-end labeling, by DNA agarose gel electrophoresis, and by cell cycle analysis using propidium iodide.

Results. Both thymus weight and the number of the thymocytes decreased significantly in the rats with necrotizing pancreatitis 6 h after introduction of pancreatitis ($p < 0.02$ vs. sham operation). Neither thymus atrophy nor the thymocyte reduction was observed in rats with edematous pancreatitis. In the thymus from the rats with necrotizing pancreatitis, in situ nick-end labeling showed significant increase of apoptotic changes of thymocytes, which was also confirmed by step ladder pattern on agarose gel electrophoresis of the extracted DNA and by cell cycle analysis.

Conclusion. Thymus atrophy associated with apoptosis occurs in the rats with necrotizing pancreatitis.

¹¹C-METHIONINE METABOLISM IN THE NORMAL HUMAN PANCREAS

A. Takasu*, T. Shimosegawa, E. Shimosegawa**, J. Hatazawa, K. Kimura*, M. Fujita, A. Takayama, M. Koizumi, T. Toyota.
*Third Department of Internal Medicine, Tohoku University School of Medicine, Sendai, Miyagi 980-77, and **Department of Radiology, Akita Research Institute of Brain and Blood Vessels, Akita City, Akita 010, Japan.

Introduction. Pancreas is one of the most vigorous organs, synthesizing secretory proteins to provide digestive enzymes and proenzymes. Positron emission tomography (PET) can be used for quantifying the amino acid metabolism and protein synthesis rate. The aim of this study was to investigate the metabolism of ¹¹C-methionine in the normal human pancreas by analysing dynamic PET images and the duodenal juice.

Methods. Eight healthy volunteers were enrolled. A triple-lumen tube was indwelt in the duodenum. Dynamic PET scan was performed for 110 minutes after the intravenous injection of ¹¹C-methionine during the continuous intravenous administration of secretin 125ng/kg/hr and caerulein 30ng/kg/hr. The radioactivity in the pancreas was measured over the PET images. In parallel, ¹¹C radioactivity in the 10 min-fractions of duodenal aspirate was measured, in the HClO₄ precipitable protein and supernatant, respectively. In addition, protein, amylase, trypsin, bicarbonate concentration were also measured in every fraction.

Results. After iv injection, ¹¹C-methionine accumulated in the pancreas in a few minutes. It remained at a plateau until the end of scanning. The radiolabelled protein in the duodenal juice increased linearly 30 min after ¹¹C-methionine injection.

Conclusion. ¹¹C-methionine is taken up rapidly by the human pancreas and is utilized for protein synthesis with kinetics similar to that of L-leucine as shown by in vitro pulse-chase studies of guinea pig slices. The ¹¹C-methionine PET may be used as a noninvasive method for estimating the functional cell mass of the human exocrine pancreas.

EFFECT OF IS-741, A NEWLY SYNTHESIZED ANTI-INFLAMMATORY AGENT, ON EXPERIMENTAL SEVERE ACUTE PANCREATITIS

J. Tamba, F. Nakamura, T. Saotome, Y. Okumura, Y. Shintani, U. Yashuoka, H. Inoue, Y. Fujiyama and T. Bamba
Department of Internal Medicine, Shiga University of Medical Science, Shiga, Japan

Introduction. Severe acute pancreatitis causes multiple organ failure (MOF) and polymorphonuclear leukocyte (PMNL) is thought to be involved in the pathogenesis. On the other hand, activation and migration of PMNL is augmented by the adhesion to vascular endothelial cells via adhesion molecules expressing on them. It has been reported that IS-741, a newly synthesized agent inhibits the PMNL extravascular migration to inflammatory sites. In the present study we examined the effect of IS-741 on experimental acute pancreatitis. **Method.** IS-741, N-(2-sulfonylumino-5-trifluoromethyl-3-pyridyl) carbamate is given by Ishihara Industry Co. (Shiga, Japan). Closed duodenal loop (CDL) was made in Wistar male rat weighing 250g as a model for severe acute pancreatitis. IS-741 was injected subcutaneously (10mg/kg) 6 times in an hour interval when the CDL pancreatitis was made. The rats were sacrificed 6h later. Pancreatic and lung wet weight, amount of ascites, myeloperoxidase (MPO) activity in lung tissue were evaluated and histological findings of pancreas and lung tissue were also examined. To investigate extravascular infiltration of PMNL, PMNL adhesion to human umbilical vein endothelial cell (HUVEC) was examined in the presence or absence of IS-741. Further the expression of ICAM-1 and ELAM-1 on HUVEC and of Mac-1 and LFA-1 on PMNL were investigated by means of ELISA and flow cytometry. **Results.** Edema of lung but not pancreas was improved by the administration of IS-741. IS-741 also reduced amount of ascites and MPO activity in lung tissue. Improvement of inflammatory changes in lung and pancreas of the rats treated with IS-741 were also confirmed histologically. The expression of Mac-1 on PMNL was inhibited by IS-741, however no change was seen in the expression of other adhesion molecules. **Conclusion.** In the present study it has demonstrated that IS-741 improved CDL pancreatitis and inhibited the extravascular PMNL infiltration by down-regulation of Mac-1 expression. Taken together it suggested that IS-741 would be a new therapeutic of acute pancreatitis.

A STUDY OF MUCIN-PRODUCING TUMOR OF THE PANCREAS

M.TANAKA, M.YAMAMOTO, H.TAKEYAMA, Y.NAKAMURA, T.HAYAKAWA, T.MANABE

First Department of Surgery, Nagoya City University Medical School, Nagoya, Japan

Introduction. We investigated the surgical indications of mucin-producing tumors of the pancreas from the view points of the clinical diagnosis, pathological findings and operative methods.

Patients and Methods. We performed surgery on 20 patients (12 men and 8 women) with mucin producing tumors of the pancreas during the period January 1988 through December 1997. Their ages ranged from 44 to 80 yr (mean age, 61 yr).

Results. Pathological assessment revealed 11 mucinous cyst adenomas, 4 mucinous cystadenocarcinomas (including one borderline case), 2 invasive mucinous cyst adenocarcinomas, one intraductal papillary adenoma, one intraductal papillary adenocarcinoma and one hyperplasia.

With regard to the operations, 3 cases underwent pancreaticoduodenectomy, 8 pylorus preserving pancreaticoduodenectomy, 6 distal pancreatectomy, 2 biopsies operation, and one enucleation of the cyst.

We could pre-operatively diagnose 5 cases as carcinomas. Two were diagnosed by endoscopic biopsy, 1 because of a fistula to the common bile duct and 2 because of the metastatic liver tumors or invasion to the retroperitoneum and portal vein. We have experienced no recurrence except in 2 biopsied cases and one patient died from another disease.

Conclusion. Operative therapy for mucin-producing tumors of the pancreas is warranted because of their potential to progress and the difficulties in differentiative diagnosis of benign and malignant lesions.

PALLIATIVE TREATMENTS FOR UNRESECTABLE MALIGNANT BILE DUCT OBSTRUCTION

J. Tanaka, H. Andoh, T. Furuya, Y. Asanuma, K. Koyama.

Department of Surgery, Akita University School of Medicine, Akita, Japan

Introduction Biliary decompression and endoprosthesis have been accepted as palliative treatments for unresectable malignant bile duct obstruction due to pancreatic cancer, biliary tract cancer and metastasis to hepatoduodenal ligament. The problems associated with such treatments have been reported to be infection, biliary sludge, migration of endoprosthesis, and re-stenosis by tumor growth. To overcome these problems, we adopted intracavitary irradiation and microwave tissue coagulation therapy (MCT) in combination with self-expandable metallic mesh stent (EMS).

Materials and Methods EMS (Wallstent®, Accuflex®, NT stent®, or Memotherm®) was inserted through the percutaneous transhepatic drainage (PTBD) fistula on 50 consecutive patients with malignant bile duct obstruction, including two patients who underwent endoscopic insertion. In selected patients, intracavitary irradiation using remote afterloading system (RALS) with ⁶⁰Co was combined in order to control the stenosis by tumor growth. Total dose of 32 to 48 Gy with 4 to 6 sessions of RALS was applied to each patient. Percutaneous MCT was also performed in patients with biliary stenosis by tumor growth after stenting in order to ablate the tumor and dilate the bile duct.

Results All of these patients have been followed up. Three patients suffered from biliary stenosis after EMS stenting and they were treated with MCT and/or EMS insertion. We observed no complications relating to the stent insertion, irradiation or MCT. Patients died of GI bleeding without jaundice or cholangitis, liver failure due to portal vein occlusion or multiple hepatic metastases 3 to 12 months after the stent insertion.

Conclusion Our experience shows that EMS could be easily inserted through the PTBD fistula without complications, and percutaneous transhepatic intracavitary irradiation and MCT could provide good palliation for patients with malignant bile duct obstruction.

SPECIFIC CHEMOTHERAPY FOR PERINEURAL INVASION OF PANCREATO-BILIARY TRACT CANCER WITH CONJUGATE OF ANTICANCER DRUG AND ANTI-NEURAL CELL ADHESION MOLECULE ANTIBODY

J. Tanaka, Y. Saito, T. Kusano, T. Yoshioka, K. Koyama.

Department of Surgery, Akita University School of Medicine, Akita, Japan

Introduction Perineural invasion is one of the most important prognostic factors in pancreato-biliary tract cancer, and recent reports indicate a close relationship between expression of neural cell adhesion molecule (NCAM) and cancer infiltration into the perineural space. To develop specific chemotherapy for perineural invasion, conjugate of anticancer drug and monoclonal antibody was prepared and evaluated anticancer activity and antibody activity of the conjugate in vitro.

Materials and Methods Mitomycin C (MMC) and anti-NCAM antibody conjugate was prepared with cyanogen bromide (BrCN) method. The degree of substitution was determined spectrophotometrically. A drug activity of conjugate was tested by MTT method of the growth inhibition with neuroblastoma cell line (IMR-32). Antibody activity of conjugate was examined by immunohistochemical staining with Avidin-Biotinylated enzyme complex on NCAM positive bile duct cancer.

Results Average degree of substitution in conjugate was 3.5 (mol concentration of drug / mol concentration of antibody). A drug activity of conjugate was maintained 66 to 95 % compared with same concentration of MMC solution. Antibody activity of conjugate showed the same level as that of antibody alone.

Conclusion MMC could be linked to anti-NCAM monoclonal antibody with BrCN method. The conjugate has both anticancer activity and antibody activity, therefore it can be useful for specific targeting chemotherapy in pancreato-biliary tract cancer.

INFLUENCE OF AUTONOMIC NERVE DYSFUNCTION ON EXOCRINE PANCREATIC FUNCTION AND CHOLECYSTOKININ-RELEASE IN HUMAN

Y. Tando, T. Nakamura, T. Suda.

The Third Department of Internal Medicine, Hirosaki University School of Medicine, Hirosaki, Japan

Introduction. Recent studies suggest that vagal nerve may play an important role in pancreatic exocrine function. And it has been well established that hormonal actions of gut peptides regulate pancreatic exocrine function. This interplay between neuronal and hormonal regulations on pancreatic exocrine function is still uncertain. We aimed to evaluate exocrine pancreatic function and cholecystokinin (CCK) release in patients with autonomic nerve dysfunction (AND).

Patients and Method. In 34 patients with diabetes (16 had AND), 26 patients with chronic pancreatitis (7 had AND), 6 patients with neurological disease (all had AND) and 8 healthy subjects, we studied pancreatic exocrine function by Secretin test. And test meal-stimulated CCK release were measured by radioimmunoassay. Autonomic nerve function of patients were evaluated with Tilting test, RR interval on electrocardiography, pilocarpine test and clinical symptom.

Results. Patients with AND of each group had a decreased pancreatic secretion in volume, bicarbonate output and amylase output. Basal CCK levels were not significantly different in patients with AND and patients without AND. However, CCK release in response to the test meal significantly increased in patients with AND.

Conclusion. We conclude that patients with AND have pancreatic exocrine dysfunction, and that a significant increase of postprandial CCK secretion in patients with AND compensates for this pancreatic exocrine dysfunction.

DEVELOPMENT OF REGULATORY RECEPTORS IN THE PANCREATA OF RATS

C Tang¹, I Biemond², ESM Jonge de-Muller, CBHW Lamers²

¹Department of Gastroenterology, The First Hospital, Chongqing University of Medical Sciences, Chongqing, P R China. ²Department of Gastroenterology, Leiden University Hospital, Leiden, The Netherlands.

Introduction. Regulatory peptides are involved in the growth of pancreas. However, little is known about the development of regulatory peptide receptors in pancreas. Receptors for cholecystokinin (CCK), bombesin (BBS), secretin, vasoactive intestinal peptide (VIP) and epidermal growth factor (EGF) were therefore visualized and quantified by storage phosphor autoradiography in rat pancreas at various ages. **Method.** The pancreata of three rats in each of age group (10 days, 1 month, 3 months, 6 months and 12 months) were removed and rapidly frozen at -80°C . Tissue sections were incubated with each labelled peptides mentioned above at concentration of 100 pM. Alternate slides were incubated with addition of 1 μM of the corresponding non-radioactive peptides to determine the extent of non-specific binding. **Results** The specific binding of CCK (3.8 ± 0.6 fmol / mg protein) and BBS (1.2 ± 0.3 fmol / mg protein) in the pancreata of rats was able to be visualized at the age of 10 days and kept increasing with their aging. The highest binding for CCK and BBS at the age of 12 months was 40 ± 0.9 and 4.6 ± 0.7 fmol / mg protein separately. The pancreata of rats at the age of 10 days expressed receptors for EGF with similar binding capacity (3.6 ± 0.7 fmol / mg protein) as that at the age of 1 to 6 months (3.8 ± 1.1 fmol / mg protein). However, the EGF receptors in the pancreata of rats at the age of 12 months were significantly decreased (0.9 ± 0.3 fmol / mg protein). It could be observed that VIP and secretin receptors in the pancreata of rats increased from the age of 10 days (1.1 ± 0.4 and 0.9 ± 0.2 fmol / mg protein) and reached to the peaks at the age of 3 months (4.5 ± 1.6 and 5.1 ± 0.9 fmol / mg protein) then decreased gradually. Their lowest binding at the age of 12 months was 0.8 ± 0.2 and 0.8 ± 0.1 fmol / mg protein. **Conclusion** The binding discrepancy of various regulatory peptides in rat pancreatic development may be benefit to understand the pancreatic physiology.

SERIAL CHANGES OF TGF- β 1 AND EXTRACELLULAR MATRIX mRNA IN OLEIC ACID-INDUCED PANCREATITIS IN RATS

M. Tashiro, Y. Kihara, H. Nakamura, T. Yamaguchi, H. Yoshikawa, Y. Ogami, M. Otsuki*

^{*}Third Department of Internal Medicine, University of Occupational and Environmental Health, Japan, School of Medicine, Kitakyushu, Japan

Introduction. TGF- β 1 and extracellular matrix (ECM) are known to play an important role on the process of fibrosis. The histological alterations in human chronic pancreatitis are scarring of acinar parenchyma and diffuse fibrosis, and overexpression of TGF- β 1 and ECM gene has been observed in the pancreas. Furthermore, transgenic mice overexpressing TGF- β 1 is shown to develop massive pancreatic fibrosis. The pathogenesis, however, remains unclear. In the present study, we investigated the serial changes of gene expression of TGF- β 1 and ECM (fibronectin, type I, III and IV procollagen) of the pancreas in oleic acid-induced pancreatic rats.

Method. Pancreatitis was induced by a single intraductal infusion of 50 μl oleic acid in male Wistar rats weighing 200-250 g. These rats were killed at 1, 2, 4, 6, 8, and 12 wks after intraductal infusion. Total RNA was extracted from the pancreas using acid guanidinium thiocyanate-phenol-chloroform method. Expression of TGF- β 1 and ECM genes was determined by Northern blot analysis. Immunoreactivity of fibronectin and type III procollagen in the pancreas was assessed by using the labelled streptavidin biotin method.

Results. TGF- β 1 mRNA expression was detectable at 1 wk after oleic acid treatment and reached the peak value at 2 wks. Fibronectin, type I, III and IV procollagen mRNA expression was detected at 1 wk and reached the peak value at 2 wks after the treatment. On immunohistochemistry, fibronectin and type III collagen immunoreactivity was observed at 4 wks. Fibronectin immunostaining was found around the tubular complexes, whereas type III collagen immunostaining was detected around small vessels as well as around the tubular complexes in the pancreas.

Conclusion. Increased expression of TGF- β 1 at 1-2 wks after oleic acid treatment was coincided with that of ECM. These results suggest that TGF- β 1 plays an important role on pancreatic fibrosis in the early stage of oleic acid-induced pancreatitis in rats.

PANCREAS PRESERVATION BEFORE ISLET ISOLATION WITH THE TWO-LAYER COLD STORAGE METHOD

Y. Tanioka, T. Deai, I. Matsumoto, Y. Suzuki, Y. Kuroda.

First Department of Surgery, Kobe University Medical School Kobe, Japan

Introduction: Poor islet yield from cold preserved human pancreas is one of the impediments to successful islet transplantation. New preservation methods to give islet yield and function similar to fresh pancreas are needed. A two-layer method (TL), which utilizes perfluorochemical (PFC) and UW solution, has previously demonstrated to have the unique characteristic of supplying oxygen to the graft, more effectively maintaining viability of whole pancreas transplants. We tested the feasibility of TL for pancreatic preservation prior to islet isolation in a canine model.

Methods: Excised dog pancreases were preserved in 4 different conditions (3 and 24 hrs of TL and simple cold storage in UW (s-UW)), then digested by the method of Ricordi and purified with COBE cell-separator. Pancreases processed immediately after procurement were the control group (without preservation). Purified islets were autotransplanted into the liver via a mesenteric vein. Yield after purification was converted to islet equivalents (IE). Maintenance of normoglycemia (<150 mg/dl) for at least 10 days after transplantation or a K-value of intravenous glucose tolerance test (IVGTT) at 3 weeks after transplantation $<1.0\%$ was considered as functional success and as a measure of islet viability.

Results: $p < 0.05$

Preservation method (hr)		Post-orientation		Functional success rate
		IE/g pancreas	IE/Body Weight(kg)	
TL	3	5600 $\pm$ 1400	12200 $\pm$ 4400	83% (n=6)
(UW/PFC)	24	4000 $\pm$ 1600	8400 $\pm$ 3300	56% (n=9)
s-UW	3	4700 $\pm$ 1800	11000 $\pm$ 3600	33% (n=6)
	24	1300 $\pm$ 1100	2800 $\pm$ 2400	0% (n=9)
without preservation	0	5000 $\pm$ 1900	10500 $\pm$ 3600	89% (n=6)

Conclusion: TL maintained islet yield and viability for at least 24 hrs in more than half the cases. In contrast, s-UW for as little as 3 hrs reduced islet viability and 24 hrs s-UW made islet yield too low for any success. TL is clearly more effective than conventional simple cold storage in UW for pancreatic preservation prior to islet isolation. Clinical trials with TL are warranted.

NEITHER REDUCED BETA CELL MASS NOR ADDITIONAL BETA CELL MASS INFLUENCE THE BETA CELL FUNCTION AND GLUT2 EXPRESSION IN PANCREATIC BETA CELLS IN RATS

Y. Tazawa, Y. Ogawa, Y. Umeda, M. Ishigame, N. Hasegawa, T. Nakamura, T. Suda.

Hiroaki Univ. School of Medicine, Hiroaki, Japan

Introduction. The etiology of type 2 diabetes is very complicated and not entirely clarified. However, both deteriorated insulin secretion and insulin resistance are related with the development of diabetes. The reduction of insulin-producing beta cells were often seen in type 2 diabetic patients by autopsy. Such reduction might be the basic defects that lead glucose intolerance. On the other hand, the reduction of glucose transporter 2 (GLUT2), a key factor for glucose-induced insulin secretion, was seen in some diabetic animals.

Methods. We investigated if the amount of beta cells would affect the beta cell function or GLUT2 expression in beta cells. The following 3 groups were prepared: 1) 50% pancreatectomized (Px) rats at 6 weeks 2) The rats transplanted 1000 islets under the renal capsule at 6 weeks 3) control rats. At 10 weeks, oral glucose tolerance test (OGTT) were performed in each group. Then the islets were isolated and perfused to study their function. And some islets were homogenized for GLUT2 immunoblotting.

Results. Daily blood glucose (BG) levels, body weight, and HbA1c levels at 10 weeks were not different among each groups. In OGTT, BG levels at 30 min were significantly higher, and serum insulin levels at 0 and 60 min were significantly lower in Px group. However, insulin secretion assessed by islet perfusion were preserved in Px group. Moreover, GLUT2 expression evaluated by Western blot were not significantly different among each group.

Conclusion. Insulin-secreting function and GLUT2 expression were not influenced by 50% Px or additional transplanted islets. In Px animals, their beta cells could compensate the reduced beta cell mass by overworking. Nevertheless, their beta cells could maintain the insulin secretion and GLUT2 expression, which suggested that the reduced beta cell mass or their overworking alone could not explain the mechanism of beta cell dysfunction often seen in diabetes.

C-JUN EXPRESSION IN PRIMARY PANCREATIC CARCINOMAS AND IN LYMPH NODE METASTASES: A PROGNOSTIC MARKER?

G Tessan, A Poletti, T Meggiato, C Ferrara, A Corsini*, G Del Favero
Dept. of Gastroenterology, *Institute of Pathology, ** Dept. of Surgery II -
Università degli Studi - Padova

Introduction. The proto-oncogene C-jun is involved in cells proliferation. Overexpression of c-jun has been described in some neoplasms as hepatocellular carcinoma, renal and lung cancer. **Aims.** 1 to evaluate the expression of c-jun protein in pancreatic cancer and in the corresponding lymph node metastases, 2. To assess the correlation of this oncogene with the histological features of the tumour and the outcome of patients. **Patients and Methods.** Surgical specimens of ductal pancreatic carcinoma of 14 resected patients and lymph nodal metastases of 8 out of them. 8 biopsies of liver metastases of subjects submitted to palliation. 5 specimens of normal pancreas from organs donors (control group). C-jun expression was determined in pancreatic tissue by immunohistochemistry (Oncogene Science, Milano). The intensity of staining was graded as follow: - neoplastic positive cells <10%, + from 10 to 30%, ++ from 30 to 60% and +++ from 60 to 90%. C-jun expression (high >30% and low <30%) was studied in relation to the patients' survival (<12 months=short-term and >12 months=long-term survivors), stage, architectural and cytological grading and vascular, lymph node, perineural invasion by Fisher's exact test. **Results.** In the normal pancreas the c-jun staining was found in less than 10% ductal cells. The percentage of tumour cells stained was increased as compared to the control group in 11/14 cases. Of the lymph node analysed only one was negative as the corresponding primary tissues. In 4 cases the tumour was more stained in the corresponding lymph node than in the primary site and in one was more stained in the primary site than in lymph nodal tissue. All liver metastases exhibited c-jun expression. All high c-jun protein expression was more frequently found in liver metastases than in pancreatic cancer tissue ($p=0.037$). The frequency of high or low c-jun expression was not different in relation to stage, architectural and cytological grading, lymph node, vascular and perineural invasion. The frequency of c-jun expression was more elevated in the group of short-term as compared to long-term survivors ($p=0.03$). **Conclusions:** 1 c-jun protein is overexpressed in pancreatic cancer, 2 its expression is not related to the histological parameters, but it seems to have a prognostic value.

SPHINCTER OF ODDI INDUCTION OF TRANSIENT PANCREATIC DUCT OBSTRUCTION IN COMBINATION WITH STIMULATED PANCREATIC EXOCRINE SECRETION RESULTS IN ACUTE PANCREATITIS IN AUSTRALIAN POSSUMS

J. Toouli, J.W.C. Chen, A. Thomas*, C.M. Irvine, A.C. Schlotzke and G.T.P. Saccone
Departments of Surgery and Histopathology*, Flinders University of South Australia, Adelaide, Australia 5042.

Sphincter of Oddi (SO) dysfunction has been implicated in some cases of acute idiopathic recurrent and biliary pancreatitis. However no direct evidence for the role of the SO in producing acute pancreatitis (AP) exists. **AIMS:** To (1) characterise a possum model of AP based on pancreatic duct (PD) ligation plus stimulation of pancreatic exocrine secretion, (2) determine if transient obstruction of PD by increased SO activity, plus stimulated pancreatic exocrine secretion, will induce AP. **METHODS:** Anaesthetised possums ($n=26$) were studied. SO manometric activity and blood pressure were continuously monitored and serum collected hourly for amylase estimation. The first group of experiments comprised: sham operation ($n=5$), PD ligation (fixed PD obstruction) alone ($n=4$); PD ligation + secretin ($n=4$); PD ligation + cholecystokinin-octapeptide (CCK) + secretin ($n=5$); PD decompression + CCK + secretin ($n=4$). In 3 other groups, the SO received multiple applications of topical carbachol (carbamylcholine) (total: 417 ± 179 nmoles) to produce SO hyperactivity resulting in PD obstruction for 5 hours: carbachol alone ($n=6$); carbachol + PD decompression; carbachol + CCK + secretin ($n=4$). CCK and secretin were given as graded intravenous boluses $0.5-5 \mu\text{g/kg}$ (each), half hourly. On completion, animals were euthanased and the pancreas harvested for histological diagnosis of pancreatitis using a scoring system. Statistical analysis utilized ANOVA and repeated measures ANOVA. **RESULTS:** Sham, PD ligation alone and PD decompressed groups were not associated with hyperamylasaemia. Fixed or carbachol stimulated transient PD obstruction plus stimulated pancreatic exocrine secretion was associated with $1.4-2.4$ fold increase in amylase ($P<0.05$) and a higher histological score for pancreatitis ($P<0.05$). These effects were not seen if the PD was decompressed.

CONCLUSION: Transient PD obstruction by increased SO activity, in conjunction with elevated pancreatic exocrine secretion induces AP. This possum model is appropriate for the study of early pancreatitis secondary to SO dysfunction and biliary pancreatitis.

ENDOSCOPIC MANAGEMENT OF PANCREATIC PSEUDOCYST - EMPHASIS ON A SIMPLIFIED TECHNIQUE.

Achut Trivedi* and S.S.Sharma

Department of Gastroenterology, S.P.Medical College, Bikaner, India

Introduction:- Endoscopic Management of Pancreatic Pseudocyst is being increasingly reported from all over the world. Most of the reports emphasize on management with the help of radiology control. We present our experience of management of pancreatic pseudocyst without radiological help in 29 patients.

Methods:- 32 patients of pancreatic pseudocyst (18 male, 14 female), with a mean age of 33.3 years (3-45 years) were subjected to endoscopic drainage. 23 patients were subjected to endoscopic cystogastrostomy (ECG), 6 to endoscopic cystoduodenostomy (ECD) and 3 to transpapillary drainage (TPD). Both ECG and ECD were done without any radiological help. A dilator cum needle knife papillotome was used for puncture of the bulging pseudocyst. Just after puncture and seeing the gush of fluid in the stomach and duodenum dilator was advanced inside the cyst while needle was withdrawn. Intracystic location of the dilator was confirmed by aspirating around 20 ml of the cystic fluid, following this stenting was done over the guidewire which was passed through the dilator. Seven french teflon stent with flaps were used. No radiological help was taken for the procedure.

Results:- Aetiology of pseudocysts included: acute biliary pancreatitis (15), Alcoholic pancreatitis (8), trauma (7) and unknown (2). In all patients ECG and ECD resulted in complete disappearance of the cyst within one month. Complications were seen in 2 patients which included haemorrhage (1) and perforation in one, both were managed surgically. Mean followup of these patients was 19.8 months while initial 15 patients had a mean followup of 34.1 months. Only 1 patient had recurrence during the followup and was managed endoscopically. ERCP was done after disappearance of cyst in 21 patients. It was normal in 15 patients of acute biliary pancreatitis group, revealed changes of chronic pancreatitis in 2 patients of alcoholic group while 4 patients of post trauma group had pancreatic duct block in head region without any symptom.

Conclusion:- This simplified single step method of cystogastrostomy and cystoduodenostomy is very helpful in management of pancreatic pseudocysts and obviates the need for radiology.

INHIBITION BY ADRENOMEDULLIN OF REGULATED AMYLASE SECRETION FROM RAT PANCREATIC ACINI

T.Tsuchida, H.Ohnishi*, T.Mine, T.Fujita.

Department of Internal Medicine IV, University of Tokyo School of Medicine, Tokyo, Japan.

Introduction. Adrenomedullin (AM) is a novel hypotensive peptide isolated from human pheochromocytoma and has recently been localized to PP cells of pancreatic islet. According to the theory of pancreatic islet-acinar axis, peptides present in pancreatic islet cells have various action on exocrine pancreas. Thus, we investigated the effect of AM on regulated exocytosis of exocrine pancreas.

Methods and Results. (1) We examined the effect of AM on CCK-stimulated amylase secretion from enzymatically isolated rat pancreatic acini. AM inhibited 100pM CCK-induced amylase secretion in a dose-dependent manner by 52% at maximum and IC_{50} was 1.1pM. (2) In order to exclude the antagonistic action of AM to CCK receptor, we examined the effect of AM on the binding rate of ^{125}I -CCK to isolated acini. AM did not affect the ^{125}I -CCK binding rate to isolated acini. (3) AM also inhibited amylase secretion induced by $1 \mu\text{M}$ calcium ionophore A23187, suggesting that AM functions at step(s) distal to intracellular calcium mobilization. (4) In streptolysin-O permeabilized acini, 10nM AM shifted the calcium dose-response curve to the right, suggesting that AM inhibited calcium-triggered amylase secretion by decreasing calcium sensitivity of pancreatic exocytosis. (5) Pretreatment with pertussis toxin (PTX) disappeared the inhibitory effect of AM on CCK-stimulated amylase secretion.

Conclusion. Adrenomedullin inhibits regulated amylase secretion by reducing the calcium sensitivity of pancreatic exocytosis. A pertussis toxin-sensitive G-protein(s) is also involved in this mechanism.

EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY AND ENDOSCOPIC TREATMENT OF PANCREATIC DUCT STONES IN PATIENT WITH SYMPTOMATIC CHRONIC PANCREATITIS

S.Tsuchiya, T.Yamaguchi, T.Ishihara, T.Hara, Y.Hatton, T.Hirano, H.Oono, T.Tsuyuguchi, H.Sasbo.

First Department of Internal Medicine, Chiba University School of Medicine, Chiba, Japan.

Introduction. Extracorporeal shock wave lithotripsy (ESWL) is a useful tool for fragmenting pancreatic duct stones. However, ductal clearance of calculi is relatively poor in patients with main pancreatic duct (MPD) strictures. In those cases, endoscopic interventions are effective in extracting stone fragments and decompressing MPD pressure. The aim of this study is to evaluate the outcome of ESWL and endoscopic treatment.

Patients and Method. Between 1991 and 1997, 63 patients with symptomatic chronic pancreatitis underwent ESWL with or without endoscopic interventions. ERP was performed in all patients before and after the treatment. We evaluated technical results, stone clearance, immediate and long-term pain relief, stone recurrence.

Results. In all patients, ERP showed MPD stones with proximal dilatation. MPD stricture was found in 26 patients. ESWL was performed prior to endoscopic interventions. Complete clearance of stones was observed in 23 patients and partial clearance in 22 patients after ESWL. Immediate pain relief and reduction of MPD diameters were obtained in 21 patients by ESWL alone. In 24 patients, interventional endoscopy was undertaken in addition to ESWL. Endoscopic extraction by using Dormia-type basket was done in 6 patients. Naso-pancreatic drain to clear the duct of remaining fragments in 13 patients and pancreatic stent for dominant stricture of MPD in 9 patients. Complete clearance of stones was achieved in 15/24 patients and immediate pain relief was obtained in all patients by additional endoscopic treatment. Patients were followed for a median of 26.4 months (range 3-74). 9/34 patients had recurrent stones after a median of 11.8 months (range 2-35) and 8/45 patients had recurrent pain after a median of 11.5 months (range 2-30).

Conclusions. ESWL is an effective treatment for fragmenting pancreatic duct stones. Endoscopic interventions increase the clearance rate of stone fragments and clinical improvement.

20 CASES OF PANCREATOLITHIASIS

< MAINLY ABOUT 6 CASES TREATED BY ESWL+EP(S)T + BALLOON DILATION METHOD (EPD-BD) >

T. Tsuji, JS. Won, H. Sasaki, M. Tamiya, N. Tsurumi, Y. Hoshino, * M. Katoh**

Department of Internal Medicine, Urawa Municipal Hospital, Urawa, Saitama, Japan. *

Department of Internal Medicine, Fukaya Redcross Hospital, Fukaya, Saitama, Japan. **

We have treated 20 cases of pancreatolithiasis in these 6 years. 1 case; by endoscopy only, 7 cases; by ESWL only, 12 cases; by ESWL+endoscopy.

Small stones (<10mm) were successfully broken into tiny fragments and removed only by ESWL.

When large stones (>10mm) were packed in the high pressure pancreas duct, EPST and EPD-BD combined with ESWL were necessary to prevent epigastralgia caused by re-packing of broken fragments.

Endoscopic Pancreatic Duct Balloon Dilation (EPD-BD) was performed in 7 cases. Narrow segments of duct were dilated by EPD-BD, then fragments were removed easily. No major problems occurred after this procedures.

ESWL combined with EPST and EPD-BD has turned out to be very useful for pancreatic stone treatments.

MODULATION BY CHEMICALS OF PANCREATIC DUCT CARCINOGENESIS IN HAMSTERS

M. Tsutsumi*, K. Iki, H. Sakitani, and Yoichi Konishi
Department of Oncological Pathology, Cancer Center, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634, Japan

The pancreatic duct carcinoma stands out as a highly lethal neoplasm associated with the poorest likelihood of survival among all major malignancies. Therefore, basic research related to modulating factors contributing to enhancement and/or inhibition of carcinogenesis in the experiment is important.

We have studied modulation of pancreatic duct carcinogenesis in two different experimental models, one featuring a classical initiation-promotion protocol with N-nitrosobis(2-hydroxypropyl)amine (BHP) or N-nitrosobis(2-oxopropyl)amine (BOP) initiation followed by administration of test compounds and the other a rapid production for pancreatic carcinomas by initiation with BOP and selection of initiated cells by augmentation pressure and then expose to agents to be tested. The induced ductal lesions in these two experimental models demonstrate a histogenesis from duct epithelial cell hyperplasia through atypical hyperplasia to intraductal and invasive adenocarcinomas. The main difference between these two protocols is that duct epithelial hyperplasia is already present in the rapid production case when application of test compound is commenced. To evaluate the effects of different compounds, incidences and numbers of lesions are quantitatively assessed.

We found deoxycholic acid, lithocholic acid, and combined cholecystectomy and lithocholic acid to enhance pancreatic carcinogenesis with the classical protocol, and Trp-P-1 exerted promotion with the rapid production protocol. Compounds which inhibited the development of lesions were the anti-oxidants, butylated hydroxyanisole (BHA), catechol and analogs, as well as sarcophytol A in the classical model and sulfation inhibitors for BOP, β -carotene, green tea polyphenol, and auroaptene in the rapid production protocol. Compounds which might have been expected to cause inhibition but did not show any beneficial effects were N-(4-hydroxy-phenyl)retinamide (4-HPR), palm carotene, lycopene and NSAIDs like aspirin and piroxicam.

These results provide useful information for further studies of possible chemoprevention, specifically of pancreatic duct carcinomas.

AN ANIMAL MODEL OF AUTOIMMUNE PANCREATITIS USING NEONATAL THYMECTOMIZED MICE IMMUNIZED WITH CARBONIC ANHYDRASE

K. Uchida, K. Okazaki, T. Chiba.

Department of Gastroenterology and Hepatology, and Endoscopy, Faculty of Medicine, Kyoto University, Kyoto, Japan

Introduction. It had been reported that an autoimmune mechanism may be involved in some patients with idiopathic chronic pancreatitis, which could be called as "autoimmune pancreatitis". We have reported that autoantibodies against carbonic anhydrase II (CA-II) were identified in some of these patients. However, it is still unknown whether CAII plays an important role in the pathogenesis or not. To clarify it, we established an animal model of autoimmune pancreatitis using neonatal thymectomized mice immunized with CA-II.

Materials and Methods. Eight Balb/c mice in each group were thymectomized on the 3rd day after birth (3dT_x). At the period of 8 weeks old, mice were subcutaneously immunized with 0.1mg of CA-II with complete Freund's adjuvant, and sacrificed after twice booster injections. Normal mice immunized with or without antigens and 3dT_x-mice injected with adjuvant alone were served as controls. Antibodies against CA-II were serially measured. We studied histological findings of the pancreas, salivary gland and liver, and the subsets of infiltrating lymphocytes by immunohistochemistry and flow cytometric analysis. Gene expressions of IFN- γ and IL-4 were also analyzed by RT-PCR.

Results. Histological studies showed degenerative changes of acinar cells in seven and infiltrating lymphocytes around the pancreatic duct in four of eight 3dT_x-mice immunized with CA-II. Infiltration of lymphocytes into the duct of salivary gland or biliary duct was found in all immunized mice. Flow cytometry and immunohistochemical studies showed predominant infiltration of CD4 positive cells in each immunized mouse. Expression of IFN- γ was predominantly detected by RT-PCR.

Conclusion. An animal model of autoimmune pancreatitis using neonatal thymectomized mice immunized with CA-II seems to be useful in clarifying the pathophysiology of autoimmune pancreatitis. Our findings suggested that an autoimmune mechanism against CAII may be involved in the pathogenesis of this animal model.

CLINICAL EVALUATION OF ASYMPTOMATIC HYPERAMYLASEMIA

MUEDA

Fukuwatari Hospital, Takebe Town, Japan.

Introduction. Technological advance in serum amylase assay (enzymatic method using autoanalyzer) made it possible to measure the enzyme activity accurately, reliably and rapidly. More than 90% of Japanese hospitals use this method now. Moreover, many hospitals employ total amylase assay as a laboratory routine test on admission. The chance finding of hyperamylasemia is sometimes hard to evaluate, thereby I conducted the following study.

Patients and Method. Total serum amylase activities were examined by an enzymatic method in 320 apparently healthy subjects >60 years of age (Group I) and in the same number of younger adults (18-59 years of age) (Group II).

P-type isoamylase assay, lipase assay, amylase isozyme on cellulose acetate electrophoresis, pancreatic ultrasonography were performed in 27 individuals in Group I and in 38 subjects in Group II who displayed hyperamylasemia. CT scan was performed in 12 in Group I and in 8 in Group II who exhibited P-type hyperamylasemia.

Results. Total serum amylase levels in Group I (73.5 ± 61.0 IU/L) were significantly higher than those in Group II (138.8 ± 45.5 IU/L, $P < 0.01$). When 220 IU/L was taken as the upper limit of normal, 19.4% of Group I and 5.3% of Group II had values in excess of this upper limit. Macroamylasemia was confirmed in one of 27 in Group I and in two of 38 in Group II. In Group I, ultrasonography showed minor changes in 4 cases. All considered of no significant clinical importance. CT scan was eventually normal in all cases examined. In Group II, none of them revealed abnormal findings either on ultrasonography or on CT scan examined.

Conclusion. Asymptomatic hyperamylasemia should be examined for P-type isoamylase activity and amylase isozyme on cellulose acetate electrophoresis first. After excluding macroamylasemia by electrophoresis, further examination of pancreas should be performed only for remaining patients who have P-type hyperamylasemia. Aging should be considered one of the causes of hyperamylasemia of unknown etiology.

A NEWLY ESTABLISHED CELL LINE FROM A PANCREATIC DUCTAL ADENOCARCINOMA INDUCED BY BOP IN HAMSTER

N.Ueda*, H.Takeyama, M.Takayama, Y.Okada, Y.Akamo, T.Manabe

First Department of Surgery, Nagoya City University Medical School, Nagoya, Japan

Introduction. The Pancreatic adenocarcinoma presents a major clinical problem. For development of new treatments, we need adenocarcinoma cell lines and experimental model which mimic the human pancreatic ductal adenocarcinoma.

Methods. Syrian golden hamsters (females, 5-6 weeks of age) received a subcutaneous injection of N-nitrosobis(2-oxopropyl)amine (BOP) at 70mg/kg. The hamsters then received further injections of BOP at 20mg/kg three times at two week intervals. Twenty weeks after the first injection, the hamsters were sacrificed by cervical dislocation and their pancreases were excised. Tumor nodules in the pancreas were divided into two, one embedded in paraffin for H-E staining and the other minced for primary culture. The cloning cylinder technique was applied to obtain clones and aliquots of 1×10^6 cells were inoculated into the subcutaneous tissue or the pancreas of hamsters. The resultant tumors were excised for histological examination.

Results. The incidence of gross tumors in the pancreas induced by BOP subcutaneous injection was 85% (6 of 7 sacrificed hamsters). Primary culture was performed for a large nodule. After about the 20th passage, we got epithelioid without fibroblast cells. After the 50th passage, its doubling time was 18 hours and when 1×10^6 cells were inoculated into the subcutaneous tissue or pancreas of hamsters, tumor nodules grew to about 5 mm in diameter after 14 days. The cell line has now been maintained in culture for more than one year.

Conclusion. We have established a pancreatic ductal adenocarcinoma cell line in hamsters which is, biologically and morphologically, closely similar to human pancreatic ductal adenocarcinoma. It should therefore prove useful for development of treatment modalities

THE ROLE OF PANCREATITIS-INDUCED ASCITIC FLUID IN THE MECHANISM OF HEPATOCELLULAR INJURY DURING SEVERE ACUTE PANCREATITIS. AN IN VIVO ^{31}P & ^{23}Na NMR STUDY

T. Ueda*, H.S. Ho², Y. Takeyama¹, and C.F. Frey²¹ The First Department of Surgery, Kobe University School of Medicine, Kobe, Japan and ² Department of Surgery, University of California at Davis School of Medicine, Davis, CA, USA

Introduction. It has been suggested that humoral mediators are involved in the mechanism of multiple organ failure in acute pancreatitis. We also showed that pancreatitis-induced ascitic fluid (PAF) from a canine model had a lethal effect on healthy rats injected with PAF. In this experiment, *in vivo* ^{31}P and ^{23}Na NMR spectroscopy was used to study the potential mechanism of hepatocellular injury associated with severe acute pancreatitis

Methods. The changes in hepatic ATP hydrolysis (inorganic phosphate, P_i) and cytosolic phosphorylation potential ($\beta\text{-ATP}/\text{P}_i$) and intracellular pH (pH_i) and intracellular Na^+ concentration ($[\text{Na}^+]_i$) in the rats after 2 h following the onset of severe necrotizing pancreatitis induced by deoxycholic acid (DCA) were compared to those in healthy rats at 3 and 6 h after intraperitoneal injection of PAF obtained from DCA-pancreatitis rats.

Results. In the liver of rats with 2 h of DCA-pancreatitis, $\beta\text{-ATP}$ decreased to 48% of baseline, and P_i increased to 174% of baseline activity. Hepatic $[\text{Na}^+]_i$ increased to 78 mM ($p < 0.05$) along with a decrease in pH_i (6.76, $p < 0.05$). When PAF was injected into the peritoneal cavity of healthy rats, it induced hepatocellular injury with similar severity. At 3 h after the injection of PAF the hepatic $\beta\text{-ATP}/\text{P}_i$ ratio decreased to 0.49, the $[\text{Na}^+]_i$ increased to 43 mM ($p < 0.05$) and the pH_i decreased to 7.30 ($p < 0.05$). At 6 h after PAF injection, the hepatic $\beta\text{-ATP}/\text{P}_i$ ratio decreased to 0.34 ($p < 0.05$), the $[\text{Na}^+]_i$ was 51 mM ($p < 0.05$), and the pH_i was 7.05 ($p < 0.05$).

Conclusions. Acute pancreatitis causes dramatic changes in hepatocellular bioenergetics and ionic metabolism, and PAF contains factor(s) inducing these changes. Our data suggest that these changes in the liver early in the course of severe acute pancreatitis may be involved in the mechanism of multiple organ failure associated with this disease

PREVENTION OF PANCREATITIS INDUCED BY ENDOSCOPIC SPHINCTER DILATION WITH THE USE OF TEMPORARY PANCREATIC STENT PLACEMENT

N. Ueno*, T. Aizawa*, Y. Ozawa**

* Department of Gastroenterology, Jichi Medical School, Yakushiji, Tochigi, Japan

** Department of Gastroenterology, Oyama Municipal Hospital, Tochigi, Japan

Introduction. We report the first case managed with temporary placement of endoscopic stents in the pancreatic duct across the papilla of Vater to eliminate suspected partial obstruction to outflow of pancreatic juice.

Case Report. A 63-year-old woman with a history of cholangitis occurring three times within the recent ten years was referred to our institution from a private clinic. Endoscopic retrograde cholangiopancreatography (ERCP) demonstrated five stones measuring 12 mm in maximal diameter in the common duct. After obtaining informed consent, therapeutic ERCP with ESD using a Maxforce 5-French balloon-tipped biliary catheter (Microvasive, Boston, MA) with a total length of 180 cm and balloon length of 3 cm (maximal diameter 8 mm) was conducted. The balloon was inflated manually with radiopaque contrast medium and saline to a maximal pressure of 8 atmospheres. Slight oozing was only observed after the dilation procedure. Thereafter, a 0.018 inch guidewire (Pathfinder; Boston Scientific Co., Ltd., Boston, MA) was passed through the diagnostic cannula into the bile duct after obtaining a pancreatogram. A 5-French, 50 mm stent with side-holes (Green Pancreatic Stent; Wilson-Cook Corp., Winston-Salem, USA) was then passed over the guidewire and placed across the papilla of Vater. Simultaneously, a 6-French, biliary stent with a length of 20 cm (Solopass; Microvasive, Boston, MA) was placed into the bile duct across the papilla of Vater. There were no complications or clinical symptoms associated with these procedures. The serum amylase levels decreased from 175 IU/l (before the procedure) to 147 IU/l (morning after the procedure) (normal range: 100-320 IU/l). Three days after the procedure, these stents were removed endoscopically and the stones were completely cleared with 2 subsequent ERC sessions.

Conclusion. Although our report is limited to a single case, temporary pancreatic stenting has potential to prevent post-procedural pancreatitis by facilitating temporary pancreatic drainage. To establish the reliability of this procedure, further prospective and randomized trials are needed.

PANCREATITIS INDUCED BY ENDOSCOPIC SPHINCTER DILATION AND THE CHANGES IN SERUM AMYLASE LEVELS AFTER THE PROCEDURE

N. Ueno*, Y. Ozawa**

* Department of Gastroenterology, Jichi Medical School, Tochigi, Japan

**Department of Gastroenterology, Oyama Municipal Hospital, Tochigi, Japan

Introduction. The short-term safety of endoscopic sphincter dilation (ESD) remains to be defined. We prospectively investigated the rate of pancreatitis and changes in pancreatic enzyme values induced by ESD.

Patients and Methods. One hundred nine patients with common bile duct stones were treated using ESD between July 1995 and September 1997. Serum amylase values were examined before and after the procedure in 102 patients treated 106 times and these findings were compared with the incidence of pancreatitis. Patients were classified into three categories according to serum amylase levels before therapy (A group: within the normal range, B group: over the normal range up to 500 mU/ml, C group: above 500 mU/ml). The severity of pancreatitis was categorized into four grades (minimal: abdominal pain after the procedure lasting no longer than the next morning, mild: with elevation of amylase values to at least three times normal and abdominal pain necessitating treatment for three nights after the procedure, moderate: required 4-10 nights treatment, severe: required intensive care).

Results. Serum amylase levels after the procedure in groups A and B were elevated significantly compared with baseline levels. In contrast, levels in group C decreased. Overall, amylase levels after the procedure were elevated in 95 studies. Minimal or mild pancreatitis developed in 21 (15 minimal and 6 mild) patients from groups A and B only. The absolute values of serum amylase levels after the procedure in patients who developed mild pancreatitis were significantly higher than those in patients who did not develop pancreatitis.

Conclusions. Although pancreatic serum enzymes were elevated in almost all patients after ESD, procedure-related pancreatitis developed in a small percentage. Among indications for this procedure, there does not seem to be any contraindication regarding treatment of patients with high amylase levels, although such patients sometimes have stone-related pancreatitis or may be predisposed to developing this disorder.

PANCREATIC CARCINOMA ASSOCIATED WITH CHRONIC PANCREATITIS

H.Wakasugi, A.Funakoshi, H.Iguchi, M.Takase, M.Inoue, Y.Soe.
National Kyushu Cancer Center, Fukuoka, Japan

Introduction. Patients with chronic pancreatitis are reported to have a somewhat higher prevalence of pancreatic carcinoma than the general population. Furthermore, recognition of carcinoma in patients with chronic pancreatitis is reported to be difficult.

Patients and Method. We investigated 7 cases of chronic pancreatitis with pancreatic carcinoma treated at our hospital to clarify clinical features of such patients.

Results. The incidence of pancreatic carcinoma in association with chronic pancreatitis was 3.6% of 196 chronic pancreatitis patients encountered over 26 years (1972-1997). The mean age of these 7 patients was 57.9 years old. Five patients (3 men and 2 women) had calcific pancreatitis and 2 patients (men) had non-calcific pancreatitis. Pancreatic diabetes had been recognized in 4 calcific pancreatitis patients. Large pancreatic stones in the head of the pancreas were recognized in two rather younger (49- and 42-year-old) women. These two patients did not habitually drinking or smoking. Almost all of the 7 patients including the women complained of continuous intractable abdominal and/or back pains or abdominal discomfort, somewhat different from the complaints in the previous period. Pancreatic tumor was suggested by imaging examinations performed in response to those complaints. However, it seemed to be difficult to obtain a definitive diagnosis earlier, because of the presence of chronic pancreatitis. Considerable calcification was shown within and around the mass lesion in the pancreas in one patient, while a cystic mass was detected in one of the others. Serum CA19-9 levels were retrospectively noted to have been elevated compared with previous data in one patient, while serum elastase 1 levels were transiently elevated on an earlier exam in one of the other patients. Radical surgery (PD) was performed only in two patients with carcinoma of the papilla of Vater. Median survival of the 7 patients was 8 months from their admission date.

Conclusion. In conclusion, early diagnosis of pancreatic carcinoma is often difficult even in patients with chronic pancreatitis who have been followed for quite a long time. The following points should alert the physician to perform more detailed examination: continuous severe pain differing from previous attacks of pancreatitis, weight loss, and changes in laboratory data, especially tumor markers such as serum CA19-9, pancreatic enzymes such as serum elastase 1.

BACTERIAL LIPOPOLYSACCHARIDE IN THE INDUCTION OF EXPERIMENTAL PANCREATITIS IN RODENTS.

MI Vaccaro*, MA Dagrosa, MA Devaux, JL Iovanna, DO Sordelli.
University of Buenos Aires, Argentina, and INSERM U315, Marseille, France.

Introduction. A possible cause-effect link between the presence of lipopolysaccharide (LPS) in the bloodstream and the appearance of acute pancreatitis has been suggested. This study was designed to assess the effect of LPS administration on different acute pancreatitis markers using rodent experimental models. **Materials and Methods.** Male, Wistar rats weighing 180-200 g, were fasted for 16 h and then received 4 intra peritoneal injections containing 10 mg/kg *Salmonella* LPS at 1 h intervals. Control rats received sterile nonpyrogenic saline. Rats were exsanguinated and the pancreas removed at 6, 12, 24, 36, 48, 72 h and 4 d after LPS administration. Pancreatitis-associated protein (PAP) expression was assessed by vertical SDS-PAGE in 12.5 % gels and Western blot analysis. In other series of experiments, male, 25-30 g Swiss mice received the same treatment as rats. Mice were also sacrificed at different times thereafter, the pancreas was removed and RNA was extracted, purified and separated by electrophoresis. Genic expression of TNF- α was established by Northern-blot analysis using a TNF- α probe labeled with 32 P. **Results.** Plasma amylase activity was significantly increased in LPS-treated rats when compared with control animals (2.712 ± 258 vs. 1.533 ± 87 U/L, $n=8$, $p<0.001$). Rat PAP was detected in the pancreas 6 h after LPS administration, it was increased at 36, 48 and 72 h, then decreased and became undetectable by 4 d after LPS administration. Expression of mouse TNF- α mRNA was apparent 1 h after LPS administration, increased by 2 h and were still high 6 h after LPS administration. There was no TNF- α mRNA expression in control mice. **Conclusion.** This study demonstrated that administration of LPS can induce experimental acute pancreatitis and suggested that the inflammatory response in the pancreas may be involved in the early pathogenesis of the disease.

PLASMA TRYPSINOGEN ACTIVATION PEPTIDE (TAP) IN EXPERIMENTAL ACUTE PANCREATITIS IN RATS

Y. Wang, S.Naruse, M.Kitagawa*, H.Ishiguro, Y.Nakae, H.Ieda, O.Ito, Y.Seki, SHK Ko, T.Yoshikawa, N.Mizuno, M.Mori, N.Nakajima, T.Hayakawa

Department of Internal Medicine II, Nagoya University School of Medicine, Nagoya 466-8560, JAPAN

Introduction. Trypsinogen activation peptide (TAP) is a sensitive indicator for the activation of trypsinogen. Urinary TAP is reported to be a useful marker for the prediction of severity of acute pancreatitis. In the present study, we measured plasma TAP in experimental pancreatitis in rats and evaluated the usefulness of measuring plasma TAP.

Materials and Methods. Edematous pancreatitis was induced by intraperitoneal injections of 40 μ g/kg of caerulein (two times). Hemorrhagic pancreatitis was induced by an infusion of 0.5 ml of 0.1% trypsin and 5% sodium taurocholate. Plasma TAP was measured by ELISA.

Results. In caerulein induced pancreatitis, plasma TAP increased 1 h after the first injection of caerulein, and then decreased to pre-pancreatitis levels. The mean value of plasma TAP at 1h (2.55 ± 0.82 nM) was significantly higher than that at 0 h (0.62 ± 0.32 nM). A subcutaneous injection of CCK antagonist (TS-941 3 mg/kg) after caerulein significantly inhibited the elevation of plasma TAP at 1 h. In trypsin-taurocholate induced pancreatitis, plasma TAP at 1 h was 41.88 ± 10.66 nM. Plasma TAP decreased gradually, but remained at significantly higher levels (18.81 ± 4.76 nM at 12 h) than pre-pancreatitis levels. The treatment with a synthetic trypsin inhibitor (ONO3403 1 mg/kg) significantly decreased the elevation of plasma TAP in trypsin-taurocholate induced pancreatitis.

Conclusion. Trypsinogen activation immediately after the induction of pancreatitis by caerulein can be detected by measuring plasma TAP. Plasma TAP can be used for estimating the severity of pancreatitis and the effectiveness of the treatment.

ISLET CELL TUMORS OF THE PANCREAS – A STUDY OF 26 CASES IN TAIWAN

H-P Wang, C-S Yang, M-S Wu, J-T Lin*, T-H Wang

Departments of Internal Medicine, Emergency Medicine and Pathology, College of Medicine, National Taiwan University, Taipei, Taiwan.

Introduction: Islet cell tumors of pancreas are rare. Functioning tumors are characterized of the symptoms induced by the hormones they secrete. In nonfunctioning tumors, hormone production is not clinically evident. So the clinical behaviors are quite different.

Methods: We reviewed islet cell tumors of pancreas in the National Taiwan University Hospital from 1978 to 1996. 26 islet cell tumors totally with 7 nonfunctioning tumors, 17 insulinomas and 2 gastrinomas were found.

Results: Patients with nonfunctioning islet cell tumors consisted of 5 women and 2 men. The mean age was 46.1 years. Abdominal pain, fullness, and body weight loss were the most frequent presentations. While patients with functioning islet cell tumors had a mean age of 45.7 years and manifested as symptoms resulted from the hormones they secreted, such as conscious change induced by hypoglycemia. Both of the nonfunctioning and functioning islet cell tumors were mostly located in the tail of pancreas (6/7 and 14/19). No abnormality of laboratory data nor elevated tumor markers were found in nonfunctioning tumors. One of our patient with gastrinoma had MEN (multi-endocrine neoplasia) type I. Angiography had good sensitivity (10/12) for functioning tumors and all showed hypervascular tumors. 5 malignancies (5/7) were found in these 7 nonfunctioning tumors, which had local invasiveness or with either liver or lymph node metastasis. 2 malignancies were found in functioning tumors, including one malignant insulinoma (1/17) and another malignant gastrinoma (1/2).

Conclusions: Even with malignant tendency, both of nonfunctioning and functioning tumors had good prognosis after adequate surgical removal.

EXPERIENCE OF COMBINED CHEMO-RADIO THERAPY IN UNRESECTABLE ADVANCED CARCINOMA OF THE PANCREAS.

S.Watanabe, H. Maguchi, N. Yanagawa, M. Osanai, K. Takahashi, T. Katanuma, H. Itoh, J. H. Kang, H. Maekubo

Center for Gastroenterology, Teine-Keijinkai Hospital, Sapporo 006, JAPAN

Purpose: Simultaneous combination treatment with chemotherapy (FAP therapy) and radiotherapy was studied in unresectable pancreatic cancer.

Patients and Method: 17 patients (43~73 yrs old, male 12, female 5), with stage IV advanced pancreatic cancer were studied. Seven patients already had distant metastasis. 5-FU (375mg/m²) was used by continuous 24 hour drip infusion on day 1 to 5, 8 to 12, 15 to 19. ADM (25mg/m²) was bolus-injected on the first day only and CDDP (40mg/m²) was used by continuous 24 hour drip infusion (FAP therapy). The whole regimen was repeated twice.

Radiotherapy, using 6.0 MeV Linac, 1.7 Gy a day (total 51 Gy/30 fractions) was used concomitantly with chemotherapy. The total period, including one week of no drug period, was seven weeks.

Results: CR was obtained in 5, PR in 9 and NC in 3 as primary lesion response. However, this regimen was effective only for the cases with local invasion. The metastatic lesions had a tendency of getting worse during the treatment.

Conclusion: The treatment of unresectable advanced pancreatic cancer has not yet been established. Combination therapy with simultaneous use of FAP therapy and radiotherapy showed an excellent response rate in locally advanced pancreatic cancer. But this regimen could not reduce distant metastatic tumor.

AN IMMUNOHISTOCHEMICAL STUDY ON VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) IN ISLET TRANSPLANTATION

H. Watanabe, S. Sumi, T. Urushihata, S. Iwasaki, G. Xu, Y. Inoue, M. Teramoto, M. Itakura, S. Yano, Y. Nio, K. Tamura.

First Department of Surgery, Shimane Medical University, Izumo, Japan

Introduction: Islet transplantation (Tx) may require neovascularization process for better and longer function. VEGF known as the most potent angiogenic factor is reportedly detected in normal islet cells. Therefore, VEGF may play a role in neovascularization of transplanted islet. We investigated the expression of VEGF in the transplanted islet cells to test the above hypothesis.

Methods: Transplantable islets were isolated from Lewis rats (8 to 10 weeks of age) by discontinuous dextran gradient after collagenase digestion. Seven hundred to 1200 islets were injected into the interscapular subcutaneous tissue (SC, n=10) or portal vein (PV, n=7) of the same descent rats. In SC group, interscapular tissue was resected 1 or 4 weeks after Tx. In PV group, the liver was resected 1 hour, 1 week or 4 weeks after Tx. Each tissue was fixed in formaldehyde and embedded in paraffin as 2-3 mm thick slices (4 or more slices for each tissue). Continuous 4 µm slice was immunostained for either insulin or VEGF using specific antibody. Normal pancreas and islets immediately after isolation were also prepared and immunostained in the same manner.

Results: In SC group, insulin-positive cell was not detected in any slices. In PV group, several insulin-positive islets were found in the portal vein 1 hour after Tx and near the surface of the liver 1 or 4 weeks after Tx. In general, islets of 1 or 4 weeks postTx were fewer in number than islets of 1 hour postTx. The islets immediately after isolation were insulin-positive and VEGF-positive as was seen in the islets of normal pancreas. Only a part of insulin-positive islets of 1 hour postTx seemed weakly stained for VEGF. However, islets of 1 or 4 weeks postTx were not stained for VEGF.

Conclusion: VEGF is detected in the islets of normal pancreas and immediately after isolation. However, it was not detected in the islets 1 or 4 weeks after Tx. VEGF produced by islet cells does not seem to play a role in islet neovascularization at least shortly after Tx. Moreover, isolated islets may lack some function which is normally exerted by islets in the pancreas tissue.

MEASUREMENT OF WATER-SOLUBLE VITAMINS AND TRACE ELEMENTS IN PATIENTS WITH CHRONIC PANCREATITIS

Taku WATANABE¹⁾, Teruo NAKAMURA¹⁾, Yusuke TANDO¹⁾, Akinori TERADA¹⁾, Naoko YAMADA¹⁾, Asako KAJI¹⁾, Toshihiro SUDA¹⁾, Ken-ichi IMAMURA²⁾, Hiroaki KIKUCHI³⁾
The 3rd Department of Internal Medicine, Hirosaki University School of Medicine, Hirosaki, Japan¹⁾.

Imamura Clinic, Hirosaki, Japan²⁾. College of Nursing and Medical Technology, Hirosaki University, Hirosaki, Japan³⁾.

Introduction: Fat-soluble vitamin deficiencies have been known in chronic pancreatitis (CP) patients. However, serum water-soluble vitamin and trace element levels remain unknown. To clarify whether or not there are water-soluble vitamin and trace element deficiencies in CP patients, we measured water-soluble vitamins and trace elements of the CP patients, subdividing into two groups (without or with steatorrhea). **Patients and Methods:** The subjects of the study were CP patients (n=26) (consisting of 16 cases without and 10 cases with steatorrhea) and healthy subjects (n=30). Blood samples were collected in the morning before breakfast. We measured serum vitamin B1, vitamin B2, vitamin B12, folic acid and serum iron, copper, zinc, magnesium, and selenium.

Result: Undernutrition was present in about 50% of CP patients with steatorrhea and about 30% of CP patients without steatorrhea. Moreover, the serum levels of vitamin B2 and selenium in CP patients with steatorrhea were significantly lower than both those in CP patients with steatorrhea and in healthy subjects. Furthermore, in several cases CP patients with steatorrhea, the serum levels of vitamin B2, iron, copper, zinc, and magnesium were low under -2SD of healthy subjects.

Conclusion: We must take the deficiencies of water-soluble vitamins and trace elements into consideration in CP patients in spite of manifest deficiency symptoms.

DETECTION OF K-RAS MUTATIONS AT CODON 12 IN THE DUODENAL ASPIRATE FOR THE SCREENING OF PANCREATIC AND BILIARY CANCER

H. Watanabe*, A. Ha, Y. Hu, K. Ohtubo, Y. Yamaguchi, Y. Motoo, T. Okai, and N. Sawabu
Department of Internal Medicine, Cancer Research Institute, Kanazawa University, Kanazawa, Japan

Introduction. We have previously reported that the detection of K-ras mutations (KRM) in the pure pancreatic juice aspirated from the orifice of papilla Vater through cannula endoscopically is useful for the diagnosis of pancreatic cancer. This study was undertaken whether the detection of KRM in the duodenal aspirate (DA) which is an easily collectable sample would be useful for the screening of pancreatic and biliary malignancy or not.

Materials and Methods. DA was obtained from 27 patients with pancreatic cancer, 24 with chronic pancreatitis, 6 with biliary tract cancer, 10 with adenomyomatosis of gallbladder, 12 with cholecystolithiasis, and 9 with no detectable diseases. DA immediately after ERCP was aspirated using duodenal endoscope without the secretory stimulation by secretin. DNA was extracted from the DA. KRM at codon 12 in the DA was analyzed by PCR-RFLP. Mutant allele specific amplification (MASA), and PCR-hybridization protection assay (HPA).

Results. Incidence of KRM in the DA with pancreatic cancer was 42%(5/12) by PCR-RFLP, 63%(17/27) by MASA, and 42%(5/12) by PCR-HPA. That with chronic pancreatitis was 25%(4/16) by PCR-RFLP, 29%(7/24) by MASA, and 19%(3/16) by PCR-HPA. Moreover, that with biliary tract cancer was 33%(2/6) by PCR-RFLP, 50%(3/6) by MASA, and 0%(0/6) by PCR-HPA. On the other hand, KRM was all negative by PCR-RFLP and PCR-HPA in the DA from patients with adenomyomatosis of gallbladder, cholecystolithiasis, and no detectable diseases. The incidence of KRM in DA with pancreatic cancer was lower than that (78% by PCR-RFLP and 66% by PCR-HPA) in the pure pancreatic juice with secretory stimulation by secretin. However, the relatively high percentage of KRM in the DA with pancreatic and biliary cancer was found by MASA which is a highly sensitive method.

Conclusion. Detection of KRM in DA is useful for the screening of pancreatic and biliary cancer using a sensitive method such as MASA.

CELLULAR MECHANISMS OF PANCREATIC INJURY BY ETHANOL AND ITS NONOXIDATIVE METABOLITES.

J. Werner¹, K. Z'graggen¹, C. Fernández-del Castillo¹, K. B. Lewandrowski², M. Laposata², D.W. Rattner¹, A.L. Warshaw¹.
Departments of Surgery¹ and Pathology², Massachusetts General Hospital and Harvard Medical School, Boston, USA.

Introduction. Recent studies have demonstrated that fatty acid ethyl ester (FAEE), nonoxidative metabolites of ethanol, mediate the early ethanol induced pancreatic changes. Nevertheless, the mechanism by which alcohol and its metabolites injures the pancreas remains unknown. We therefore compared the effect of different treatment agents in ethanol and FAEE induced pancreatic injury.

Materials and methods. Ethanol or FAEE were infused into male Sprague-Dawley rats (n=12 per subgroup). Six different treatment regimens (2 protease inhibitors; (1) soybean trypsin inhibitor (STI), (2) gabexate mesilate (GAB); 2 oxygen free radical scavengers; (3) 4-Hydroxy-TEMPO (4-HT), (4) catalase; a xanthine oxidase inhibitor; (5) allopurinol; and a calcium channel blocker; (6) verapamil) were infused parallel to ethanol and FAEE in additional animals and the effects were compared to saline control animals. Pancreatic injury was assessed at 6 and 12 hrs by wet-dry ratio (edema), plasma and tissue levels of trypsinogen activation peptide (TAP), and by light microscopy. FAEE- and ethanol-levels in serum were measured by gas-chromatography mass spectroscopy.

Results. Ethanol infusion led to generation of plasma ethanol and FAEE levels equivalent to those seen in intoxicated individuals. Ethanol and FAEE, but not the saline controls, induced highly significant edema formation ($p < 0.001$), TAP ($p < 0.001$), and vacuolization of pancreatic acinar cells. The two protease inhibitors reduced pancreatic TAP formation in both ethanol and FAEE induced injury ($p < 0.01$), but did not reduce pancreatic edema. 4-HT, catalase and allopurinol decreased both edema formation and TAP in ethanol and FAEE induced injury ($p < 0.05$). Verapamil reduced edema in ethanol, but not in FAEE induced injury, while TAP was reduced in both ($p < 0.01$). Vacuoles in pancreatic acinar cells observed in all treatment groups were identical to those found in the untreated control animals.

Conclusion. This study shows that ethanol and FAEE induce a pancreatitis-like injury in rats which can be reduced by protease inhibitors, oxygen free radical scavengers, and calcium channel blockers. Thus the mechanism of ethanol and FAEE induced injury to the pancreas seems to be identical and includes dysregulation in these different steps.

SPECIFIC THERAPY OF LOCAL AND SYSTEMIC COMPLICATIONS OF ACUTE PANCREATITIS WITH MONOCLONAL ANTIBODIES AGAINST ICAM-1.

J. Werner¹, K. Z'graggen¹, C. Fernández-del Castillo¹, K. B. Lewandrowski², C.C. Compton², A.L. Warshaw¹.

Departments of Surgery¹ and Pathology², Massachusetts General Hospital and Harvard Medical School, Boston, USA.

Introduction. The outcome of severe acute pancreatitis is dependent on its pulmonary and septic complications. Leukocyte adhesion and infiltration are central events in the pathogenesis of necrotizing pancreatitis. The aim of the present study was to analyze the time point and levels of the expression of adhesion molecules in the pancreas and lung in pancreatitis of different severity and to assess whether treatment with a monoclonal antibody against ICAM-1 can reduce local and systemic complications.

Methods. Expressions of ICAM-1 in pancreas and lungs was investigated in 80 male Sprague-Dawley rats at 3, 6, 12, and 24 hours after induction of mild edematous (caerulein 5 µg/kg/h i.a. over 6 hrs), or severe necrotizing pancreatitis (intraductal infusion of glycodeoxycholic acid and caerulein i.a.) As assessed by immunohistochemistry and Western-blot analysis ICAM-1 expression was correlated with leukocyte infiltration (myeloperoxidase activity) and histological changes. The possible therapeutic effect of monoclonal antibodies against ICAM-1 was assessed by pancreatic and lung edema, intrapancreatic trypsinogen activation (TAP), leukocyte infiltration, and histopathology in additional animals.

Results. Increased ICAM-1 expression in pancreas was evident by 6 hours in edematous pancreatitis, but at no time point in lung. In contrast ICAM-1 was upregulated at 3 hours in the pancreas and at 12 hours in lung in necrotizing pancreatitis ($p < 0.001$). Treatment of severe necrotizing pancreatitis with monoclonal antibodies against ICAM-1 decreased both local pancreatic injury (TAP $p < 0.01$; myeloperoxidase activity $p < 0.001$; histology $p < 0.05$) and systemic lung injury (myeloperoxidase activity $p < 0.01$; histology) compared to control.

Conclusions. Increased expression of ICAM-1 precedes leukocyte infiltration in pancreatitis. Upregulation is observed only in pancreas in mild pancreatitis but in both pancreas and lung in severe pancreatitis. The therapeutic window still allows effective mitigation of both pancreatic and lung injury with ICAM-1.

CLINICAL ANALYSIS OF 30 CASES OF ACUTE EDEMATOUS PANCREATITIS CONCOMITANT HEPATIC INJURY

Xu Guo-Qiang

Gastroenterology Department, The First Affiliated Hospital, Zhejiang Medical University, Hangzhou, China.

A group of 30 patients with acute edematous pancreatitis concomitant hepatic injury were investigated. We found that almost all patients suffer from hepatic dysfunction, including elevation of bilirubin, alkaline phosphatase, transaminases. Mechanism of hepatic injury is due to release of amylopin, invasion of toxin, biliary tract dyskinesia and infection, abnormal hepatic hemodynamics and injury of free oxygen radicals, so on. This pancreatic hepatitis is easy to be diagnosed by examination of liver function, ultrasonic waves, virology. Our study indicated that hepatic injury of acute edematous pancreatitis is reversible. By treating the primary disease, hepatic function can return normal level in short time.

MALABSORPTION IN THE PATIENTS WITH PANCREATIC INSUFFICIENCY

- FROM THE ASPECTS OF BONE METABOLISM-

N. Yamada, T. Nakamura, Y. Tando, T. Watanabe, A. Kaji, T. Suda
The Third Department of Internal Medicine, Hirosaki University
School of Medicine, Hirosaki, Japan

Introduction. Recently osteoporosis is increasing among old people and causing lumbago and pathological bone fracture. It is reported that the condition of pancreatic insufficiency is sometimes complicated by pathological bone fracture. Less intake of diet including calcium and malabsorption of fat-soluble vitamins may be concerned. And then in the patients with pancreatic steatorrhea, we studied several parameters of calcium metabolism (serum calcium, vitamin D, E, and K levels) and the bone mineral content. And we evaluated their bone metabolism from the metabolism of fat-soluble vitamins.

Patients and Method. Twenty patients with steatorrhea and twenty healthy controls were studied. Serum albumin, fat-soluble vitamin contents in the blood (vitamin D, E, and K), and total cholesterol concentrations were determined. In addition, high-dosage pancreatic enzyme substitution was given to the patients with pancreatic insufficiency for some period and we studied the bone mineral content and changes in the blood fat-soluble vitamin levels were evaluated before and after the treatment.

Results. The mean vitamin E level was significantly reduced in the patients. The vitamin D and K levels had also been reduced in the patients without treatment. In some patients, the blood vitamin D level was extremely reduced. The bone mineral content showed a tendency to decrease among the patients.

Conclusion. The results indicated that the patients with pancreatic insufficiency had suffered from the deficiency of fat-soluble vitamins. As for vitamin K, the results of thrombin tests were suppressed, but clinically symptoms were not detected. And vitamin D and K had promoting effect for bone structure. From these points, it was suggested that in patients with pancreatic insufficiency, pancreatic enzyme substitution and substitution of vitamin D and K might be considered.

Platelet-activating factor antagonist TCV 309 attenuates lung injury in rats with cerulein-induced pancreatitis complicated by sepsis

Y. Yamaguchi, J. Liang, F. Matsumura, K. Okabe, H. Ohshiro, T. Matsuda, S. Nakano, K. Ishihara, M. Ogawa
Department of Surgery II, Kumamoto University Medical School, Kumamoto, Japan

The therapeutic effects of an intravenously injected platelet-activating factor (PAF) antagonist TCV309 on lung injury were studied in rats with cerulein-induced pancreatitis complicated by sepsis. Pancreatitis was induced by four intramuscular injections of cerulein (50 μ g/kg at 1-hour intervals). Pancreatitis rats were injected intraperitoneally with 10 mg/kg of lipopolysaccharide (LPS) 6 hours following the first cerulein injection as a septic challenge. Pancreatitis rats were treated with a bolus intravenous injection of TCV309 (3 or 30 μ g/kg) 30 minutes before the septic challenge. Intense mononuclear cell infiltration and lung hemorrhage occurred in pancreatitis rats with sepsis, but were not seen in pancreatitis rats receiving a bolus TCV309. The TCV309-treated rats had lower serum concentrations of cytokine-induced neutrophil chemoattractant (CINC), and lower levels of CINC mRNA in the lung, as well as fewer the pulmonary infiltrates immunoreactive for CINC or Mac-1 (CD11b/CD18). LPS-stimulated *in vitro* CINC production by naive bronchoalveolar macrophages was significantly enhanced by pretreatment with PAF. Pretreatment with TMB-8 (an inhibitor of calcium release from endoplasmic reticulum), W7 (calmodulin antagonist), pyrrolidine dithiocarbamate (PDTTC) (a potent inhibitor of NF- κ B) completely abrogated the chemoattractant production. Altered intracellular calcium, due to Ca^{2+} efflux from intracellular stores, may be involved in the 'priming' of bronchoalveolar macrophages to release CINC following triggering with LPS during acute cerulein pancreatitis. The PAF antagonist TCV309 effectively prevented pancreatitis-associated lung injury following the septic challenge.

DETECTION OF MUTATIONS OF *p53* TUMOR SUPPRESSIVE GENE IN PURE PANCREATIC JUICE OF PATIENTS WITH PANCREATIC CANCER

Y. Yamaguchi, K. Ohtsubo, Y. Hu, H. Watanabe, Y. Motoo, T. Okai, and N. Sawabu.

Department of Internal Medicine, Cancer Research Institute, Kanazawa University, Kanazawa, Japan

Introduction: Although *p53* mutations have been found in 40-76% of pancreatic cancer (PC) tissues, no reports have focused on *p53* in pure pancreatic juice (PPJ). Here, to improve the genetic diagnosis using PPJ, we tried to analyze *p53* mutations of PPJ obtained by duodenal endoscopy from patients with PC, and compare with results of analysis of *K-ras* mutations.

Materials and methods: PPJ was obtained from 26 patients with PC, 4 with mucin producing adenoma (MPA), 16 with chronic pancreatitis (CP). PPJ were collected endoscopically through canula from papilla of Vater. DNA was extracted from PPJ, and amplified by PCR for exon 5, 6, 7 and 8 of *p53*, respectively. Non-RI SSCP was used for detection of mutant bands from which were recovered for direct sequencing analysis. In the same samples, the mutations of *K-ras* gene at codon 12 were also analyzed by the methods of PCR-RFLP and hybridization protection assay (HPA).

Results: Of the twenty-six cases of PC, *p53* mutations were detected in the 11 cases (42.3%). On the other hands, no mutations were seen in the cases with MPA nor CP. In *K-ras* analysis with PCR-RFLP which had a high sensitivity in spite of some false positives, 84.0% (21/25) were mutation positive. By HPA which was a quantitative method having the advantage of high specificity for PC, mutation was detected in 65.3% (17/26). Using combination assay with *p53* and *K-ras* mutations, genetic abnormalities were seen in 92.0% with PCR-RFLP and 73.1% with HPA. In both methods, *p53* alone was positive in two cases.

Conclusions: The specificity of *p53* mutations for PC is very high, with some cases exhibiting only *p53* mutation without *K-ras* mutation. So, simultaneous analysis of *p53* and *K-ras* mutation is suggested to enhance the genetic diagnosis of PC.

INSULIN GENE TRANSFER CAN BE A NEW OPTIONAL THERAPY FOR REPLACEMENT OF PANCREAS

M. Yamaguchi*, M. Kuzume, T. Matsumoto, A. Matsumiya, H. Shimura, H. Nakano, K. Kumada

Department of Surgery, Showa University Fujigaoka Hospital, Yokohama, Japan

Introduction: A substitute for pancreas including transplanted pancreas should be provided after total pancreatectomy because it is quite difficult to control blood glucose levels with periodic insulin administration. We constructed adenovirus vector containing human insulin gene (AxIns), which was proved to produce human proinsulin enough to decrease blood glucose levels in diabetic rats. Therefore, we tested the effects of *in vivo* insulin gene transfer using AxIns on pathological changes after total pancreatectomy.

Materials and Methods: Nine Beagle dogs weighing 10-13 kg were subjected to total pancreatectomy preserving duodenum and divided into three groups which were no insulin group (n=3), periodic insulin administration group (10 units/day of long acting human insulin) (n=3), and AxIns group (n=3). AxIns of which bioactivity was 4×10^{10} PFU, was injected via the spleen immediately after total pancreatectomy. Survival periods, changes in blood glucose levels during the day, oral glucose tolerance test (OGTT) using 15 g of glucose, serum levels of human c-peptide and total protein were monitored.

Results: Mean survival periods were 2 days in no insulin group, 10 days in insulin group, and 25 days in AxIns group. Blood glucose levels and OGTT were maintained in normal range in AxIns group, but not in insulin group. Serum levels of total protein were kept at normal levels in AxIns group which were significantly higher than in insulin group ($p < 0.05$).

Conclusion: AxIns injection, but not periodic insulin administration, controlled blood glucose levels and restored serum total protein levels after total pancreatectomy. Insulin gene transfer using adenovirus vector creates the cells which can produce and secrete human proinsulin to compensate pancreatic beta cell function and can be a new optional therapy for replacement of the pancreas.

DISTAL PANCREATCTOMY WITH COMBINED RESECTION OF THE CELIAC ARTERY FOR CARCINOMA OF THE BODY AND TAIL OF THE PANCREAS

H. Yamamoto^{1,2}, Y. Nimura¹, N. Hayakawa^{1,2}, J. Kamiya¹, S. Kondo^{1,3}, M. Nagino¹, M. Kanai¹, K. Uesaka¹, N. Yuasa¹, T. Mayumi¹

First Department of Surgery, Nagoya University School of Medicine¹

Department of Surgery, Tohoku Hospital² and Kasugai municipal Hospital³

Introduction. Most of carcinoma of the body and tail of the pancreas is often unresectable when detected, because it easily invaded adjacent organs. We evaluated a distal pancreatectomy (DP) with combined resection of the celiac artery (CA) for pancreatic cancer invading around the CA.

Patients. From 1975 through 1997, we experienced 54 patients with ductal carcinoma of the body and tail of the pancreas. Thirty two of them (59.2%) underwent DP. Eight patients (5 men and 3 women) of them who underwent DP with combined resection of the CA were enrolled in this study. The mean age was 63.3 years.

Results. Appleby operation was performed in two patients because of cancer invasion to the stomach, while a DP with combined resection of the CA preserving the whole stomach was performed in the remaining six patients. The blood flow to the stomach was supplied through the right gastric and right gastroepiploic arteries. Other combined resection included adrenalectomy in 4 patients, partial resection of transverse colon in 2, left nephrectomy in 1, and portal vein resection in 3. Operative morbidity was found in 5 patients (pancreatic fistula in 3 and gastric ulcer in 2), but all complications resolved with conservative treatment. The histologic examinations revealed a moderately differentiated tubular adenocarcinoma in 5 and a well differentiated tubular adenocarcinoma in 3. Microscopic tumor invasion into the CA, splenic artery or the common hepatic artery was found in all patients. Five patients died of recurrence 4 months to 31 months after surgery, which included peritoneal dissemination in 2, liver metastasis in 2, and local recurrence in 1. Two patients are alive without any sign of recurrence 75 months and 5 months after surgery, respectively.

Conclusions. A DP with combined resection of the CA for carcinoma of the body and tail of the pancreas involving the CA is a reasonable procedure with respect to the curability. The stomach-preserving procedure would provide a better quality of life for the resected patients.

CELL PHENOTYPE OF INTRADUCTAL CARCINOMA ACCOMPANIED WITH INVASIVE PANCREATIC DUCTAL CARCINOMA

M. Yamano, H. Watanabe, K. Date, K. Nisikura, T. Fujiwara, Y. Ajioka
First Department of Pathology, Niigata University School of Medicine, Niigata, Japan

<Aim> To study cell phenotype of papillary or non-papillary intraductal carcinomas observed in and/or adjacent to invasive ductal carcinoma of common type. **<Material & Method>** We used 11 resected cases of common type invasive pancreatic ductal carcinoma with intraductal spreading, which immunohistochemically showed p53 protein overexpression. Each of the resected pancreata was cut stepwise at 4-5 mm thickness. All of deparaffinized sections of all paraffin blocks were stained with hematoxylin-eosin and MAb against p53 and Ki-67. The following stainings were performed for analysis of mucous quality of epithelial elements: diastase digestive alcian blue-periodic acid-Schiff reaction, high-iron diamine-alcian blue (pH 2.5) staining (HID-AB), and paradoxical concanavalin A for class III mucosubstances (ConA-III), MAb 45M1 and MAb MUC 2. Cytological phenotype is classified into five types as follows: gastric (GS) type (45M1⁺, ConA-III⁺/45M1⁺, ConA-III⁻), pancreatic proper-epithelium (PE) type (HID⁺, 45M1⁺, ConA-III⁻), goblet cell (GC) type (MUC 2⁺), combined (CB) type, and mucin negative (MN) type

<Results>

Number of intramucosal cancer foci examined in each case and % of phenotype

No. of foci	13	6	52	18	25	4	11	5	9	4	2
GS	100%	100%	94%	88%	84%	50%	55%	20%	22%		
GS+PE			2%	6%	16%		36%	40%		50%	
PE								40%	78%		
GE+GC						25%					
GE+PE+GC			2%		25%						
MN			2%	6%			9%		50%	100%	

<Summary & Conclusion> 91% of tumors revealed a gastric phenotype at intraductal cancer area. Intramucosal cancer foci with mucus was of low-grade cytologic atypia, and one with mucous negative was of high-grade atypia. It is suggested that most of pancreatic intramucosal cancers arise from gastric type mucous hyperplasia in a form of low-grade cytologic atypia and show progression to high-grade cancer in the mucosa with subsequent stromal invasion

PERCUTANEOUS TRANSGASTRIC PANCREATIC INTERVENTION TO CHANGE A PANCREATOCUTANEOUS FISTULA TO A PANCREATOGASTRIC FISTULA

E. Yamanouchi, H. Kawaguchi, I. Endo, H. Arakawa, T. Yamaguchi, K. Sakuyama, T. Okada*, H. Komoriyama*, I. Tanaka*, M. Hagiwara*
Department of Radiology, Department of Surgery*, St. Marianna University Yokohama Seibu Hospital, Yokohama, Japan

Introduction. Surgery was thought to be the only way to cure a pancreaticocutaneous fistula. The intent of this poster exhibit is to show as an alternative to surgery a new interventional method, a percutaneous transgastric approach, to cure a pancreaticocutaneous fistula.

Patients and Methods. Three female patients, 7 to 48 years old, underwent this interventional method of treatment. Percutaneous drainage of the pancreatic pseudocyst caused a pancreaticocutaneous fistula in two cases. Postoperative leakage from the anastomosis between the pancreas and jejunum caused a pancreaticocutaneous fistula in the other case. This method of treatment is composed of percutaneous transgastric puncture of a pancreaticocutaneous fistula and balloon dilation of the newly formed fistula between the stomach and old fistula.

RESULTS. The skin ostium of the pancreaticocutaneous fistula rapidly healed after percutaneous transgastric drainage. There has been no recurrence of the pancreaticocutaneous fistula or pancreatic pseudocyst after tract change to the gastric cavity until today for four years. No complications were observed during or after this procedure.

CONCLUSION. Percutaneous transgastric puncture to the pancreaticocutaneous fistula and balloon dilation to make a new sufficient ostium on the posterior gastric wall are quite safe and economical. This new method instead of surgery may become the first choice to cure a pancreaticocutaneous fistula.

POSTOPERATIVE HEPATIC ARTERY INFUSION CHEMOTHERAPY USING CHEMOSENSITIVITY TEST FOR PATIENTS WITH PANCREATIC CANCER

Hiroki Yamaue*, Hiroshi Tanimura, Hironobu Onishi, Yasuo Kasano, Hideki Yamoto, Yoshiharu Shono, Takuya Tsunoda, Masaji Tani, Makoto Iwahashi, Kazuhisa Uchiyama
Second Department of Surgery, Wakayama Medical School, Wakayama 640, Japan.

Introduction. We have been applying MTT assay as a chemosensitivity test, and selected the appropriate anticancer drugs for pancreatic cancer patients. In the present study, the clinical effects of postoperative hepatic artery chemotherapy according to the results of MTT assay was examined in terms of the inhibition of liver metastasis and the prolongation of survival.

Patients and Methods. Seventy-five patients were enrolled in this study. Fifty patients had pancreatic head cancer with 64% resectability rate (PD: n=26, PpPD: n=6), whereas 25 patients had pancreatic body and tail cancer with 84% resectability rate. The extended lymph node dissection has been performed, and 7 patients were received the portal vein resection. Hepatic artery infusion was performed in 18 patients, and anticancer drugs, which were selected according to the results of MTT assay, were administered via the hepatic artery.

Results. The inhibition rates were 64±31%, 66±25%, 63±31%, 61±29%, and 34±33% *in vitro* for cisplatin, mitomycin C, adriamycin, 5-fluorouracil, and VP-16, respectively, and the sensitivity for VP-16 was lower than other drugs (p<0.01). Three patients with portal vein resection who didn't receive hepatic artery chemotherapy had postoperative liver metastasis, and shorter survival (199 days, 242 days, and 240 days after surgery, which was identical to the survival of patients with curability C). On the other hand, 4 patients with portal vein resection received hepatic artery chemotherapy, and 2 patients died at Day 864 and 632 postoperatively due to the local recurrence, but not liver metastasis. Moreover, 2 patients are now surviving at Day 601 and 398 with no evidence of liver metastasis. There was a significant difference in survival between the patients with or without hepatic artery chemotherapy (p<0.05).

Conclusion. The survival might be prolonged by hepatic artery chemotherapy using MTT assay for pancreatic cancer patients.

INSULIN-LIKE GROWTH FACTOR-I (IGF-I) ACTIVATES PROTEIN KINASE B (PKB)/AKT IN PANC-1 PANCREATIC CANCER CELLS

Z. Yao, Y. Okabayashi*, K. Sakaguchi, T. Kitamura, K. Inushima, S. Kimura, Y. Yutudo, K. Kida, W. Ogawa, M. Kasuga.
Second Department of Internal Medicine, Kobe University School of Medicine, Kobe, Japan.

Introduction. IGF-I exerts various effects including cell growth, transformation and anti-apoptosis. Mediators of intracellular signaling through IGF-I include insulin receptor substrate-1 (IRS-1), phosphoinositide (PI) 3-kinase, and a serine/threonine kinase PKB/Akt. PKB/Akt, a downstream target of PI 3-kinase, consists of at least four isoforms, and amplification of PKB β /Akt2 isoform in pancreatic cancer is reported. PANC-1 cells are shown to possess IGF-I receptors, IRS-1, and PKB/Akt. In the present study, we investigated the effect of IGF-I on PKB/Akt activation in PANC-1 cells.

Methods. PANC-1 cells were grown in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum. After 48-h starvation, cells were stimulated with IGF-I and lysed in a buffer containing 1% Nonidet P-40 and protease inhibitors. Cell lysates were subjected to SDS-polyacrylamide gel electrophoresis, followed by Western transfer. Since phosphorylation of PKB/Akt at Thr308 and Ser473 results in activation of the kinase, we assessed phosphorylation of PKB/Akt by immunoblotting using phospho-specific Akt (Ser 473) antibody.

Results. IGF-I stimulated PKB/Akt activation in a concentration-dependent manner, with the maximal effect at 30-100 nM. After stimulation of PANC-1 cells with 100 nM IGF-I, activation of the kinase was observed at an early time point and was sustained. Other growth factors, cholecystokinin and bombesin failed to activate PKB/Akt in PANC-1 cells. In order to clarify the role of PKB/Akt on the biological responses to IGF-I in PANC-1 cells, we generated an adenovirus vector that contained an expression unit for wild-type and dominant negative mutant of PKB/Akt. Using these adenovirus vectors, we investigated the effect of dominant negative PKB/Akt on anchorage-dependent and -independent growth of PANC-1 cells in response to IGF-I. These results will be discussed.

Conclusion. IGF-I activates PKB/Akt in PANC-1 pancreatic cancer cells.

THE ROLE OF INTERLEUKIN-1 β CONVERTING ENZYME IN ACINAR CELL APOPTOSIS AFTER PANCREATIC DUCT LIGATION IN MICE

H. Yasuda, K. Kataoka, M. Moriguchi, M. Kato, K. Kashima, H. Ichimura*, T. Iida*, M. Kita*, and J. Imanishi* Third Dept. of Internal Medicine and Dept. of Microbiology*, Kyoto Prefectural University of Medicine, Kyoto 602, Japan. **Introduction.** Recent it has been reported that pancreatic acinar cell apoptosis occurs in the gland with experimental acute pancreatitis. Although Fas and Fas ligand participate in apoptosis of several organs, the mechanism of acinar cell apoptosis is little known. We have shown the intrapancreatic expression of both Fas and Fas ligand mRNA after pancreatic duct ligation (PDL) in mice. In the present study, our aims were to determine the role of IL-1 β Converting Enzyme (ICE) in acinar cell apoptosis of the pancreas. **Materials and Methods.** In 5 to 11 weeks-old male ICE deficient and wild-type mice (BASF Bioresearch Corporation, MA, USA), the pancreatic duct was ligated selectively at the splenic lobe of the gland. On day 1 or 3 after PDL, the degree of pancreatic injury was evaluated by determining serum amylase activity and histological scores (edema and cell infiltration). Acinar cell apoptosis was quantified by in situ Hoechst 33342 dye staining (H-342) and TdT-mediated DNA end labeling (TUNEL) method. **Results.** On days 1 and 3 after PDL, there were no significant differences in the serum amylase activities and the histological scores between the two groups of mice. On day 3, the ratio of acinar cell apoptosis in ICE deficient and wild-type mice were $2.4 \pm 0.2\%$ and $3.3 \pm 0.5\%$ by H-342, and $2.8 \pm 0.5\%$ and $2.8 \pm 0.3\%$ by TUNEL, respectively. Acinar cell apoptosis evaluated by H-342 in ICE deficient mice was less than that in wild-type mice on day 3 after PDL, but not significant. **Conclusion.** After PDL in mice, deficient ICE did not influence the development of pancreatic injury. The present results suggest it is not only ICE that mediate acinar cell apoptosis after PDL.

EXPRESSION OF THE RNA COMPONENT OF TELOMERASE IN PANCREATIC CANCERS

K. Yashima*, N. Miura, Y. Kishimoto, J. Hasegawa, A.F. Gazdar, H. Kawasaki.

Second Department of Internal Medicine, Clinical Pharmacology, School of Medicine, Tottori University and UT-Southwestern Medical Center.

Introduction. Telomerase is an RNA-containing polymerase essential for maintaining telomere length. It is associated with cellular immortality and is expressed in the vast majority of invasive tumors.

Method. To investigate the role of telomerase expression in pancreatic cancer, we developed and applied an in situ hybridization method for the demonstration of human telomerase RNA (hTR). Using this method, we can identify the cellular expression of hTR in archival paraffin-embedded tissues. For hybridization, we used [³⁵S]UTP-labeled antisense and sense RNA probes. Sense probe was used as a negative control. The specificity of the assay was confirmed by examining sections of adult testis and colorectal carcinoma.

Results and Conclusion. We studied 24 resection specimens from 9 pancreatic cancers. Relatively high nuclear hTR expression is present in most tumors. Moreover, we are analyzing the hTR expression pattern in pancreatic tissues. These analyses may assist to understand the pathogenesis of pancreatic cancer.

PHENYLALANINE- AND BOMBESIN-CAUSED RELEASE OF CHOLECYSTOKININ ARE MEDIATED BY CALMODULIN-DEPENDENT PROTEIN KINASE AND DIACYLGLYCEROL-ELICITED PROTEIN KINASE C IN STC-1 CELLS

H. Yoshida*, M. Iida, A. Takahashi, A. Ikegami, T. Sato, J. Niikawa, S. Tanaka, K. Mitamura. 2nd Dept. Int. Med., Showa Univ., Tokyo, Japan.

Introduction. The mechanisms of release of cholecystokinin (CCK) from small intestine have been studied. Recently, a luminal CCK-releasing factor (LCRF) in rat intestinal secretion and the porcine diazepam binding inhibitor (DBI) were proposed as candidates which could activate CCK release. Bombesin (BBS) and L-phenylalanine (Phe) caused an increase in intracellular Ca^{2+} via L-type Ca^{2+} channels which resulted in release of CCK in STC-1, an established cell line derived from intestinal endocrine tumor cell in mice, as a useful model of CCK-releasing cell. We investigated the intracellular mechanisms involved in CCK release stimulated by an aromatic amino acid, Phe, which penetrates through plasma membrane, and we compared signal transduction pathways evoked by Phe to those by BBS using STC-1 cells. **Method.** STC-1 cells were grown in Dulbecco's Modified Eagle Medium with horse serum and fetal calf serum, then incubated with 1 ml of medium containing BSA and aprotinin. CCK was measured by enzyme immunoassay using anti-CCK-8-specific antiserum (OAL-656) and alkaline phosphatase (ALP)-CCK-8. The calmodulin-dependent protein kinase (CaMK) II activity was measured by ³²P-incorporation transferred from [γ -³²P] ATP using autocamtide II as the substrate. **Result.** BBS and Phe caused dose-dependent release of CCK. STC-1 cells released CCK in a time-dependent manner during stimulation of BBS for 120 min. W-7, a calmodulin antagonist, significantly inhibited Phe- and BBS-stimulated CCK release. Pretreatment with doses more than 0.5 μ M of KN-62, a selective inhibitor of CaMK II, significantly reduced Phe-stimulated CCK release without KN-62 in a dose-dependent manner. CaMK II activity was increased by 50 and 75 nM Phe. A maximal stimulation was observed after a 20 min-incubation with Phe. BBS, 1 nM up to 100 nM, which dose-dependently evoked CCK release, did not affect CaMK II activity. R59022 (5 μ M), the diacylglycerol (DAG) kinase inhibitor I, induced a significant augmentation of the maximal CCK release stimulated by 50 nM Phe. Staurosporine, a protein kinase C (PKC) inhibitor, significantly inhibited CCK release stimulated by both BBS and Phe. U-73122 (100 nM), an inhibitor of phospholipase C (PLC), failed to inhibit release of CCK stimulated by Phe. **Conclusion.** We conclude that release of CCK stimulated by BBS and that by Phe possessed the common signal transduction pathways mediated by DAG-activated PKC and Ca^{2+} /CaMK. The DAG involved in CCK secretion stimulated by Phe could be derived from another phospholipid except phosphatidylinositol.

THE EVALUATION OF MR PANCREATOGRAPHY FOR BILIARY AND PANCREATIC DISEASES

Masahiro Yoshida, Tadahiro Takada, Hodaka Amano

First department of surgery, Teikyo university school of medicine, Tokyo, JAPAN

MRCP is recently developing non-invasive imaging method to depict biliary and pancreatic duct. In this paper, we evaluated the ability of MRCP how to demonstrate the pancreatic duct image.

[Materials] 33 patients were received MRP (pancreatic carcinoma 11 cases, chronic pancreatitis 5, bile duct ca. 5, pancreato-biliary maljunction 3, gallbladder ca. 2, bile duct stone 3, Papillar Vater ca. 2, liver tumor 2).

[Methods] (1) Put surface coils to the ventral and dorsal side with supine position. MR apparatus is Fast SE, TR/TE/NEX: 9000msec-12000/200-300/2, FOV 16-20cm, Matrix: 256×256 with GE Signa Advantage 1.5T. Breath synchronization or holding method were used. (2) The image of pancreatic duct was classified into three types. (a) Fine; clear, and could be evaluated, (b) Fair; clear, but could not be evaluated, (c) Poor; The image was unclear. (3) Diagnostic ability in quality was examined pancreatic stone and pancreatic cancer.

[Results] (1) Pancreatic duct could be demonstrated in 30 cases out of 33 cases, and evaluation of duct was possible in 23 cases. (2) 11 cases of pancreatic carcinoma and 2 cases of pancreatic stones were able to be diagnosed through MRP

[Conclusion] Visualization ability of pancreatic ducts could be pleased in this time. And, in particular, MRP was more useful with the case after operation which pancreatic ducts could not be examined by endoscopic examination.

MUCIN PRODUCING TUMOR OF PANCREAS - 2 CASES

Masahiro Yoshida, Tadahiro Takada, Hodaka Amano

First department of surgery, Teikyo university school of medicine, Tokyo, JAPAN

Mucin producing tumor of the pancreas (MPT) is a clinical concept characterized with swelling of Papilla Vater, associated with a marked mucin secretion from the orifice and dilatation of main pancreatic duct. However, this tumor is frequently accompanied by carcinoma, adenoma and hyperplasia. This paper will demonstrate two cases of mucin-producing intraductal adenoma and adenocarcinoma.

[case 1] 83 year old man. He was admitted to our hospital complaining of upper abdominal pain and back pain. Abdominal Helical Computed tomography and magnetic resonance pancreatography revealed branched pancreatic duct type MPT. Pyrolosis preserving pancreatoduodenectomy was performed. Pathological examination revealed branched duct type intraductal papillary adenoma.

[case 2] 54 year old man. He was admitted to our hospital complaining of nausea and vomiting. Helical CT and MRP revealed branched type MPT. PPPD was performed. Pathological examination revealed combined type of Intraductal papillary adenoma.

[conclusion] Helical CT, MRCP were useful for diagnosis of MPT. But, it is something difficult to distinguish between malignant and benign disease, thus we now recommend surgery for MPT.

LYMPHOEPITHELIAL CYST OF THE HEAD OF THE PANCREAS

-CASE REPORT AND REVIEW OF LITERATURE

Masahiro Yoshida, Tadahiro Takada, Hodaka Amano

First department of surgery, Teikyo university school of medicine, Tokyo, JAPAN

Lymphoepithelial cyst of the pancreas with high level of serum CA19-9 is rarely reported.

[case] 51 year old male.

In April 1996, in an annual medical examination, a low echoic abdominal tumor was revealed on the head of the pancreas by ultrasonography. He had no remarkable symptoms, family and past history.

[Laboratory data on admission] Values for tumor markers, carbohydrate antigen (CA19-9) were elevated (101.4 U/ml).

[Abdominal US, CT, MRI and ERCP] US showed a cystic lesion, 2cm in diameter in the head of the pancreas. CT and MRI revealed a multicystic mass. ERCP did not detect the cystic lesion and showed normal pancreatic duct.

[Operative findings] Tumorectomy was performed on July 29, 1996. at the laparotomy, a well circumscribed mass was seen on the neck of the pancreas. No lymph node metastasis or ascites were found. Tumor was then removed from the pancreatic tissue. No parenchymal connection between the tumor and the pancreas was noted. The cyst was covered with a thick fibrous capsule and was filled with yellowish-white keratinized material.

[Histological findings] The cyst wall was composed of mature keratinizing squamous epithelium and lymphoid tissue. It was diagnosed as a benign lymphoepithelial cyst of the pancreas.

The literature revealed 18 case reports of pancreatic lymphoepithelial cyst. Most cases indicated high level of tumor markers.

INVASIVE CARCINOMA DERIVED FROM MUCIN-PRODUCING INTRADUCTAL PAPILLARY ADENOCARCINOMA OF THE PANCREAS

Masahiro Yoshida, Tadahiro Takada, Hodaka Amano

First department of surgery, Teikyo university school of medicine, Tokyo, JAPAN

[Introduction] Mucin producing tumor of pancreas is regarded to have a low grade malignancy. However, some cases of mucin-producing intraductal carcinoma show a poor prognosis when cancer spreads into the pancreatic parenchyma.

[case] 58-year-old, a man. 20 years ago, he received a pancreatic necrosectomy due to acute necrotizing pancreatitis. After 7 years follow up, he was admitted to our department because of the huge abdominal tumor.

[examination data] A high level of CRP, CA19-9, CEA were recognized with slightly anemia on hospitalization. Abdomen CT revealed a marked enlargement of the head of the pancreas, and dilatation of pancreatic duct. Endoscopic examination showed swelling of Papilla Vater with mucin secretion from the orifice. Angiography showed the encasement of portal vein and tumor staining at the head of the pancreas. Operation was conducted under the diagnosis of invasive mucin producing cancer of pancreas with invasion for duodenum, portal vein and transverse colon, on July 29, 1996. Pancreatoduodenectomy with portal vein resection associated with the transverse colon excision was performed.

[pathological findings] Cut surface of resected specimen revealed papillary tumor in huge cyst of the head of the pancreas which was been full of mucinous liquid. Pathological examination showed invasive mucinous cystadenocarcinoma, S3, rp2, du3.

keratinizing squamous epithelium and lymphoid tissue. It was diagnosed as a benign lymphoepithelial cyst of the pancreas.

The literature revealed 18 case reports of pancreatic lymphoepithelial cyst. Most cases indicated high level of tumor markers.

SURGICAL EXPERIENCE FOR PANCREAS DIVISUM

Masahiro Yoshida, Tadahiro Takada, Hodaka Amano
First Department of surgery, Teikyo university school of medicine, Tokyo, JAPAN

Pancreas divisum is a malformation caused by malfusion of ventral pancreas and dorsal pancreas. It causes repeated pancreatitis due to elevation of dorsal pancreatic duct because Wirsung duct and Santorini duct are not communicated. For therapy of this disease, endoscopic papillotomy of the accessory papilla or stenting is usually conducted which postoperatively, in most cases, lead to recurrence of pancreatitis caused by re-stenosis. We here report on the three successful cases which we experienced through limited surgery.

Case No. 1: 35 years old male. He was admitted to our hospital because of repeated pancreatitis for 12 years. Endoscopic Santorini duct-graphy showed a marked dilatation of Santorini duct that was not communicated to Wirsung duct. This Santorini duct was found to be the main pancreatic duct from the accessory papilla to the pancreatic tail, and Wirsung duct was only drained from the ventral pancreas. He underwent duodenum-preserving pancreatic head resection (DPPHR). Reconstruction was performed through pancreatoduodenostomy. His postoperative course was uneventful. After discharge, he has not have had any recurrence of pancreatitis for 5 years.

Case No. 2: 58 years old male. He was admitted to our hospital due to repeated abdominal pain of pancreatitis for 3 years. ERCP showed a malfusion of Wirsung duct and Santorini duct, that was diagnosed as pancreas divisum. He received middle pancreatic segmentectomy.

Reconstruction was performed through pancreatojejunostomy by a Roux-en-Y. His postoperative course was uneventful. After discharge, he has had no evidence of repeated pancreatitis.

Case No. 3: 50 year old man. Heavy alcohol drinker. He was hospitalized because of severe abdominal pain after drinking of alcohol. After detailed examination, he was diagnosed as pancreas divisum. He underwent duodenum-preserving pancreatic head resection. After discharge, he has had no evidence of repeated abdominal pain and he also keep not drinking.

EFFECTS OF HETEROCYCLIC AMINES ON PANCREATIC DUCT CARCINOGENESIS INITIATED BY N-NITROSOBIS (2-OXOPROPYL) AMINE (BOP) IN HAMSTERS.

M. Yoshimoto¹, M. Tsutsumi¹, K. Wakabayashi² and Y. Konishi¹.
¹Department of Oncological Pathology, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634, Japan and ²Chemoprevention Division, National Cancer Research Institute, 5-1-1 Tsukiji, Chuo-ku, Tokyo 604, Japan.

Adenocarcinoma of the pancreatic ducts is to the fifth leading cause of cancer death in both U.S. and Japan. Development of the disease is clinically silent so that at the time of the diagnosis, the vast majority of cases are incurable with a very poor prognosis. Thus, the detection of etiological factors in the environment offer the hopes for the prevention of this deadly disease. Heterocyclic amines (HCAs) are mutagens isolated from cooked foods and their carcinogenicities were extensively studied in mice and rats. However, so far no studies have been done in hamsters. Recently, we established a rapid production model for pancreatic duct adenocarcinomas in hamsters based on the principle of the resistance of carcinogen initiated cells to the cytotoxic and cytostatic effects of carcinogens originally reported for rat liver carcinogenesis and this model is useful for studying not only the mechanisms underlying duct carcinogenesis but also for the detection of initiators or promoters for the carcinogenesis. In the present experiments, we studied the 6 HCAs of PhIP, MeIQx, IQ, Trp-P-1, Trp-P-2 and AαC which were given in the diets after the initiation and selection procedure when pancreatic duct cell hyperplasias were developed for 50 and 70 days. For 50 days administration of 0.02% Trp-P-1 increased the total numbers of ductal lesions including hyperplasia, atypical hyperplasia and intraductal or invasive carcinomas and for 70 days administration, the incidence of carcinomas increased to 67% as it was compared 33% in hamsters without receiving Trp-P-1. Furthermore, Trp-P-1 was given intragastrically at a concentration of 100 mg/kg body weight as the initiator instead of BOP increased BrdU labeling index in pancreatic duct epithelial cells. Other HCAs did not show any effects on duct carcinogenesis.

These results suggest that Trp-P-1 may be the initiator and promoter for pancreatic duct carcinogenesis in hamsters and full carcinogenicity study will be further required.

ANTITUMOR EFFECT OF PANCREATIC CANCER CELLS RETROVIRALLY TRANSDUCED WITH CYTOKINE GENES Y. Yoshida^{1,2*}, M. Tagawa², M. Kimura¹, K. Tasaki², M. Miyauchi², M. Narita^{1,2}, K. Takenaga², T. Takenouchi², S. Sakiyama², T. Yamaguchi¹, H. Saisho¹

Department of Internal Medicine(I)¹, Chiba University, School of Medicine: Chiba Cancer Center Research Institute², Chiba, Japan
Introduction. Immuno-gene therapy can be one of the approaches to improve the prognosis of pancreatic cancer patients. To test its clinical feasibility, we have examined a possible antitumor effect of human pancreatic cancer cells producing interleukin-2(IL-2), IL-4, IL-12, or IL-15 in nude mice.

Methods AsPC-1 cells, human pancreatic cancer cells, were transduced *in vitro* with retrovirus vector, LXS-N, containing a respective cloned cytokine cDNA. Transduced or parent AsPC-1 cells (1x10⁶) were injected subcutaneously or intraperitoneally into BALB/c nu/nu mice, and the tumor volume and the survival days were assessed. When cytokine-producing cells were rejected, parent cells were re-inoculated into the mice to examine whether immunity was induced.

Results. Loss of tumorigenicity of IL-2- or IL-4-producing cells was observed when they were injected subcutaneously, while the tumors of IL-12- or IL-15-producing cells showed the retardation of their growth. Inoculation of AsPC-1 cells, but not irrelevant human colon cells, into the mice which had rejected cytokine producing cells showed retarded tumor growth of the rechallenged cells. Thus, tumor specific acquired immunity was generated. The survival of the mice intraperitoneally inoculated with each cytokine producer was prolonged compared with that of the mice injected with parent cells. Moreover, intraperitoneal injection of the retrovirus bearing IL-2 gene into the mice which had parent cells in the peritoneal cavity prolonged the survival of the mice, suggesting successful *in vivo* transduction.

Conclusion. Local cytokine production from pancreatic cancer cells can induce immune response even in a T cell deficient state, and this provides a possible therapeutic strategy for pancreatic cancers.

USE OF DISPOSABLE SURGICAL STAPLER IN OPERATIVE CYSTOGASTROSTOMY FOR DRAINAGE OF PANCREATIC PSEUDOCYST

Y. Yunoki, H. Takeuchi, Y. Yasui, K. Tanakaya, E. Konaga
Department of Surgery, Iwakuni National Hospital, Iwakuni, Japan

Introduction. We present here a new practical application of the surgical disposable stapler for the operative drainage of a large symptomatic pancreatic pseudocyst.

Case Report. A 68-year-old man with a history of acute pancreatitis 1 year before was admitted with intermitted epigastralgia. CT revealed a large pancreatic pseudocyst at the back of the stomach. ERP showed no communication with the cystic cavity. Surgical treatment was proposed because direct percutaneous drainage route was not found on ultrasound. Cystogastrostomy was performed after the Jurasz's transgastric procedure. After gastrotomy of the anterior wall, Auto Suture* PREMIUM PLUS CEEA* 34 stapler (Auto Suture, Norwalk, Connecticut, USA) was fired to anastomose the cystic wall and gastric posterior wall. The patient made an uneventful recovery. He is free of abdominal symptom, and follow-up CT demonstrated a marked diminution in the size of the pseudocyst.

Conclusion. Operative cystogastrostomy using disposable surgical stapler should be listed in the options for treatment of pancreatic pseudocyst.

CIRCULATING TUMOR CELLS IN THE PERIPHERAL BLOOD OF PATIENTS WITH PANCREATIC CANCER INDICATE AN ADVANCED TUMOR STAGE

K. Zgraggen, B. Centeno, J. Werner, R.E. Jimenez, C. Fernández-del Castillo, A.L. Warshaw*

Departments of Surgery and Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, MA

Introduction: Circulating tumor cells in the peripheral blood of patients with cancer may identify patients with advanced tumor stages. We developed and evaluated a method to determine the prevalence of tumor cells in blood from pancreatic cancer patients.

Methods: Blood (10ml) was collected from 142 patients, 84 with pancreatic cancer and 58 with benign diseases (pancreatic adenomas - 19, chronic pancreatitis - 18, acute pancreatitis - 4, non pancreatic controls - 17). The mononuclear cell population was separated over a density gradient. Immunocytochemistry was performed on cytospins using a monoclonal antibody against cytokeratins (AE1/AE3). Slides were analyzed in a blinded fashion by a cytopathologist. Two-tailed Fisher exact tests and Chi-square tests were used for statistical analysis where appropriate.

Results: Circulating cytokeratin-positive cells were detected in 29% of pancreatic cancer patients. The specificity for cancer was 96% (1/58 false positive = 1.7%). 92% (24/26) of cell-positive patients had unresectable cancer. The prevalence of cytokeratin positive cells was 8% (2/26) in patients with resectable cancer versus 40% (23/58) in patients with unresectable or metastatic cancer ($p = 0.005$). Carcinomas confined to the pancreas (T1, T2) and those with a lower histologic grade (G1, G2) had a lower prevalence of circulating tumor cells (10%, 9% respectively) than advanced (27%; $p = 0.22$) and high-grade tumors (32%; $p = 0.06$). The prevalence of AE1/AE3-positive cells was 48% in patients with distant metastases and 25% in patients with apparently localized disease ($p = 0.008$) and was significantly greater in patients with peritoneal metastases (75%) than in patients with liver metastases (17%; $p = 0.012$).

Conclusion: Circulating cytokeratin-positive cells (AE1/AE3) are frequently detectable in patients with pancreatic cancer and indicate both an advanced tumor stage and a minimal chance for a potentially curative resection. The prevalence of circulating tumor cells is particularly high in patients with peritoneal carcinomatosis.

CAUSES OF DECEASE IN NECROTIZING PANCREATITIS. ANALYSIS OF 50 CASES.

N. Zarnescu, R. Costea, A. Dinulescu, S. Neagu.
Department of Surgery, University Hospital, Bucharest, Romania.

Introduction. We made a retrospective study of 50 cases of patients with necrotizing pancreatitis (NP). All these patients died and the necropsies have been performed. The purpose of the study was to identify the aggravating factors in the evolution of this disease.

Patients and method. From 1991 to 1997 50 patients died with the diagnosis of NP. Among risk factors we mention: obesity (68%), tobacco (56%), vascular disease (78%), diabetes (28%), age above 70 (12%), coexisting pathology (32%). The presence of all these factors has been statistically increase in our cases against cases with good evolution.

Results. The results of necropsies have shown in majority of cases the extensive (or almost total) aspect of pancreatic necrosis (42 cases - 84%). In 49 cases the death occurred between 1 and 14 days after surgery. One case died after one month. In 4 cases (8%) we found extensive intestinal infarctus. In 6 cases (12%) we found myocardial infarctus at patients with important sings of coronary ischemia before operation. In 28 cases (56%) we found important ascitis (26 with hemorrhage aspect and 2 with pus aspect). In 8 cases (16%) patients developed pulmonary septic complications. All cases presented MOF syndrome with important toxic signs for the cases that died early after surgery and with important septic sings for those which died in the second week. From etiologic point of view, ethanolic etiology (36 cases - 72%) have a greater frequency versus biliary etiology, in contrast with the cases with favorable outcome, where the biliary etiology is more frequently.

Conclusion. Although evolution is uncertain, there is a lot of aggravating factors: ethanol, age above 70, obesity, extension of the lesions, vascular pathology, ascitis.

PROTECT ROLE OF MULTIPLE ORGAN DYSFUNCTION SYNDROME ON ACUTE NECROTIZING PANCREATITIS WITH SOMATOSTATIN AND GROWTH HORMONE

Zhang Qunhua, Cai Duan, Ni Quanxin, Zhang Yanling

Department of Surgery, Huashan Hospital of Shanghai Medical University, Shanghai 200040, P. R. China

Introduction. To study the protect role of systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS) on acute necrotizing pancreatitis (ANP) with somatostatin and growth hormone, and evaluated the procession from SIRS to MODS and therapeutic strategies in ANP.

Methods. Rat ANP models were made by retrograde injection of 3.5% sodium taurocholate 2.5ml/kg into the pancreatic duct. Serum IL-1 β , IL-6, TNF α , Amylase, endotoxin, and albumin were examined. The morphology and pathology of the pancreas, liver, lung, heart, and kidney as well as the electromicroscopical investigation of liver, lung and heart cells were observed. Finally TNF α mRNA in the liver, lung, kidney and heart after ANP were observed by reverse transcriptase - polymerase chain reaction, and TNF α of lung, pancreas, and heart were performed by immunohistochemical staining. Efficiency of somatostatin and growth hormone were also observed in this experiment and clinical study.

Results. The results indicate that ANP develops remarkable elevation of those inflammatory mediators which are positively correlated with the development of ANP and MODS. It also demonstrates somatostatin and growth hormone can inhibit the inflammatory mediators and TNF α mRNA over expression and reduce the risk of MODS, and indicating that the liver may play an important role in protecting the host from multiple organ failure.

Conclusions. It is concluded that TNF α mRNA take in an important role in ANP progression and somatostatin and growth hormone may be the effectual treatment to prevent the development and progression of MODS on ANP in clinic.

The role of PYY in regulating the growth of human pancreatic cancer cells and its mechanism

Zhang Zhongbing, Fu Qiang, Zhang Xingrong.
Dept. of Gastroenterology, Chang Zheng Hospital, Shanghai, China.

Recently it has been reported that gastrointestinal peptide hormones may act as growth modulators of pancreatic cancer in vivo and in vitro. PYY is a 36-amino-acid peptide secreted predominantly by PYY endocrine cells located in ileum, colon and rectum and decreases pancreatic exocrine and endocrine function and pancreatic blood flow. We studied whether pancreatic cancer cell growth would be inhibited by PYY.

In this study, the effect of PYY on the growth of human pancreatic cancer cell line SW-1990 was investigated by means of cell count and ³H-TdR incorporation as parameters for cell growth. Cellular cAMP in cytosol was measured with radioimmunoassay after PYY stimulation to study the possible post-receptor signal transduction pathway. Cell mutant P53 gene mRNA and mutant P53 protein were analyzed with Northern dot blotting and immuno-histochemical method after exposure to PYY.

The results indicated that PYY significantly inhibited the growth of human pancreatic cancer cell line SW-1990 ($P < 0.01$), with a dose- and time-dependent decrease in the number of cells and ³H-TdR incorporation. In PYY treated pancreatic cells, a dose-dependent decrease of intracellular cAMP was noted ($P < 0.01$). The mutant P53 mRNA and P53 protein were significantly reduced in cells by treated with PYY compared with control cells without treatment.

The above results suggested that PYY might inhibit pancreatic cancer cell line SW-1990 cells growth via decrease of intracellular cAMP levels in vitro. In the other hand, The decrease of mutant P53 gene expressing might be one of the mechanisms by which PYY inhibited pancreatic cancer cells growth.

CHANGES OF TAP AND PROP CONCENTRATIONS IN SEVERE CASES OF PANCREATITIS

K. Honjo, S. Uehara, H. Handa, Y. Tsuji, M. Ohi, G. Kuroiwa, A. Hirayama.

Gastroenterology Department, Tonan Hospital, Sapporo, Japan.

Introduction. The activation of trypsinogens(TAP) and pancreatic type 1 phospholipase A2(PROP) have been reported in severe pancreatitis patients. Tap assays for released trypsinogen activation peptides are an accurate early indicator of severity in acute pancreatitis.

Subjects and methods. We measured TAP and PROP concentrations in plasma from 22 acute pancreatitis(AP) patients(severe 9, moderate 13), moderate chronic pancreatitis(CP) patients and 10 healthy adult controls. TAP and PROP assays were detected by ELISA(Oriental Kobe).

Results. TAP concentrations of severe AP(19.2 ± 1.3 nM), moderate AP and CP(9.8 ± 7.3) were significantly higher than that healthy controls(0.08 ± 0.05 nM). PROP concentrations of severe AP(11.0 ± 4.0 nM), moderate AP and CP(5.4 ± 1.6 nM) were significantly higher than that healthy controls(1.0 ± 0.3 nM). Over 5.0nM of TAP and PROP concentrations in approximately 90% of severe AP were presented.

Conclusion. Measurements of TAP and PROP concentrations may have important implications for the progress of severe AP.