Pancreatic Society of Great Britain and Ireland

A meeting of the Pancreatic Society of Great Britain and Ireland was held at Freeman Hospital, Newcastle upon Tyne on 18 November 1994. Dr Richard Lendrum, President of the Society, chaired the meeting. Sixteen papers and 16 posters were presented. The Rodney Smith Medal and Prize was awarded to Mr S Falconer, and the Society's Poster Prize was awarded to Mr S Wigmore.

Collagenase, stromelysin, and tissue inhibitor of metalloproteinase expression in pancreatic and ampullary cancer

S BRAMHALL, G STAMP*, N R LEMOINE*, J DUNN†, C MCCONKEY†, J NEOPTOLEMOS *(Academic Department of Surgery, City Hospital NHS Trust, Birmingham, *TCRF, Hammersmith Hospital, London, and †Clinical Trial Unit, University of Birmingham)*
Pancreatic cancer is characterised by locally aggressive behaviour and early metastasis. The matrix metalloproteinases (MMP) are a family of nine proteolytic enzymes that are capable of degrading the extra cellular matrix, and the functional activity of these enzymes is controlled by one of three specific tissue inhibitors of metalloproteinases (TIMP). There is strong experimental evidence that expression of the MMPs correlate with tumour invasion and that reduced expression of TIMPs correlate with tumour progression and metastasis.

Immunocytochemistry was performed on sections from 50 patients with pancreatic cancer (n=27), ampullary cancer (n=12), low bile duct cancer (n=3), neuroendocrine tumours (n=3), and chronic pancreatitis (n=5) using antibodies raised against the active sites of collagenase (MMP 2), two different antibodies, stromelysin (MMP 3) and tissue inhibitor of metalloproteinase (TIMP 1).

Expression of MMP 2, MMP 3, and TIMP 1 was greater in pancreatic and ampullary cancer than any other pathology ($p<0.0001$) and expression in the malignant epithelial cells in pancreatic and ampullary cancer was higher than in the stromal tissues (MMP 2 100% *v* 37%, MMP 3 93% *v* 15%, TIMP 1 93% *v* 4%, $p<0.00001$). There was strong correlation between the expression of the two antibodies for MMP 2 ($p<0.0003$), between MMP 2 and TIMP ($p<0.009$), and between MMP 3 and TIMP 1 ($p<0.0007$). TIMP 1 expression in lymph node positive patients with ampullary and pancreatic carcinoma was reduced (88% positive, 25% negative and 94% positive, 73% negative). This was significant when the two were combined ($p<0.02$). Increased expression of MMP 2 inversely correlated with tumour differentiation ($p<0.05$).

In conclusion, MMP 2, MMP 3, and TIMP 1 are strongly implicated in the invasive properties of pancreatic and ampullary cancer.

Isolation of a novel gene rearranged and overexpressed in pancreatic cancer

A MCKIE, N R LEMOINE *(Oncology Unit, Hammersmith Hospital, London)*
A novel approach has been developed to detect genomic rearrangement or deletion in tumour cells using PCR amplification of DNA with primers to the ubiquitous Alu repeat sequences scattered throughout the human genome. We have isolated a number of fragments that are affected by tumour specific rearrangement and used these as probes to identify clones from robotically gridded high density filters of pancreatic cell cDNA and genomic libraries. These clones in turn have been sequenced and used as probes for fluorescent in situ hybridisation (FISH) mapping of metaphase chromosomes and as probes for in situ hybridisation of tissue sections. One of the cDNAs isolated is a putative novel sequence, which shows frequent and specific upregulation of expression in pancreatic cancer and hence may represent a new oncogene.

Tumour specific targeting of prodrug activation as gene therapy for pancreatic cancer

N R LEMOINE, J D HARRIS, H C HURST, K SIKORA *(Oncology Unit, Hammersmith Hospital, London)*
Current treatments available for metastatic malignant disease of the pancreas and gastrointestinal tract are ineffective. One of the most promising of the selective genetic strategies against cancer is VDEPT (virally directed enzyme prodrug therapy), which uses a viral vector to carry a prodrug activating enzyme gene into both tumour and normal cells. By linking the enzyme gene downstream of tumour specific transcription units, tumour specific prodrug activation is achieved. Overexpression of the oncogene ERBB2, occurs in many pancreatic and gastric tumours and involves transcriptional upregulation of each copy ERBB2. We have constructed chimeric minigenes consisting of the ERBB2 promoter linked to cytosine deaminase or herpes simplex thymidine kinase. We have made viral particles to transduce a panel of ERBB2 positive and negative pancreatic cell lines. Significant cell death was seen for ERBB2 positive cell lines transduced with the ERBB2-CD construct and treated with the prodrug 5-FC. Cytosine deaminase activity was low in ERBB2 negative transduced cell lines but was increased at least 10-fold in ERBB positive transduced cells. This tumour cell specific cytotoxic system is currently being developed for use in a clinical protocol that could be used against tumours that overexpress ERBB2.

Cytotoxicity of lithium gamma linolenic acid on pancreatic carcinoma cell lines in vitro

D RAVICHANDRAN, A J COOPER, C D JOHNSON *(University Surgical Unit, Southampton General Hospital, Southampton)*
Lithium salt of gamma linolenic acid (LIGLA), an essential fatty acid derivative, has been reported to be effective in prolonging survival in pancreatic cancer without significant side effects. We tested the in vitro susceptibility to LIGLA of two pancreatic ductal carcinoma cell lines (Panc 1 and MIA PaCa2, ECACC, Porton Down).

Cells were grown under standard conditions (37°C, 5% co2, 100% relative humidity, in culture medium containing 10% FBS), harvested and seeded at 2500 cells in 100 µl of medium per well in 96 well cell culture plates. LIGLA (Scotia, Guildford) in 100 µl of medium was added 24 hours later to achieve final concentration varying from 5 to 140 g/ml. Control experiments were run with medium alone, lithium chloride (0·06 to 2 mmol/1) to exclude a lithium effect, and palmitic acid (PA) (4 to 140 µg/ml) to exclude a non-specific fat overload effect. Plates were kept at standard conditions, inspected daily, and removed when the cells in medium only became confluent or on the seventh day. Cell viability was assessed by a microculture tetrazolium assay.

At concentration between 10–40 µg/ml almost all cancer cells were killed. Cytotoxicity was visible within 24 hours at high concentrations and was fully developed in 72 hours. LiCL and PA showed no such changes. LIGLA had a dose and time dependant cytotoxic effect on both cell lines and may provide a useful therapeutic adjunct in patients with pancreatic cancer.

Secretin induces a paradoxical sphincter of oddi (SO) hyperpressure effect in alcoholic patients without pancreatic disease

S MOSSI, R DELREZ, I PORTAL, R LAUGIER *(Hospital de la Conception, Marseille, France)*
Secretin relaxes SO in normal controls but also in chronic pancreatitis patients who present with a basal SO dyskinesia.[1] Our aim was to study the SO activity before and after secretin injection in alcoholic patients without pancreatic disease.

Sixteen alcoholic patients (12 men, 4 women) 38·4 years ±9·1, admitted to our department for alcoholic withdrawal were included in that study. Mean daily consumption was 177·1±76·2 g/d for 17·5±5·7 years. None of the patients had a history of abdominal pain or hyperamylasemia. Pancreas, gall bladder, main bile duct were normal at ultrasonography. The main pancreatic duct pressure was normal compared with controls before and after secretin. By contrast, alcoholic patients had a greater frequency of phasic contractions to the SO (5·5±1·7 *v* 3·9±0·3/min) and showed a paradoxical response to secretin: dramatic increase of basal sphincteric tone (28·8±6·1 *v* 10·1±2·4 mm Hg) associated with an enhancement of the amplitude of phasic contractions (101·1±18·3 *v* 70·7±16·3 mm Hg).

SO dyskinesia, present in chronic pancreatitis is reduced by secretin.[1] We describe here an alcohol induced SO dyskinesia and a paradoxical effect of secretin, which loses its relaxation effect on the SO. This probably does not play an important part in the

dilatation of the main pancreatic duct seen in chronic pancreatitis but may be relevant for the pathophysiology of some alcoholic acute pancreatitis.

1 *Endoscopy* 1994; **26:** 222–7.

A double-blind placebo controlled study of lexipafant (a potent PAF antagonist) in acute pancreatitis

S W GALLOWAY, L FORMELA, A N KINGSNORTH *et al (Department of Surgery, University of Liverpool)* Platelet activating factor is a key inflammatory mediator implicated in the pathogenesis of acute pancreatitis (AP). The aim of this study was to evaluate the effects of three days of intravenous lexipafant on the clinical course and serum markers of inflammation in human AP. Eighty three patients with AP were randomised to receive either placebo (P) or active (A) medication in a double blind study. Patients were monitored daily by APACHE II scoring and measurement of serum parameters-polymorphonuclear elastase (PMNE), E-selectin (E-sel), and interleukin-6 (IL-6). The two groups were found to be evenly matched at baseline.

		Mean change from baseline (SEM)			
		Day 1	*Day 2*	*Day 3*	
APACHE II score	A	−1·0 (0·4)	−0·5 (0·4)	−1·0	(0·4)
	P	−0·5 (0·4)	0·4 (0·5)	−0·4	(0·6)
IL-6 pg/ml	A	−147·3 (66·4)	−221·5 (84·2)	−241·9	(86·6)
	P	33·4 (63·3)	−81·2 (56·7)	−124·6	(57·7)
PMNE μg/l	A	28·0 (37·7)	−3·5 (32·2)	−11·2	(34·6)
	P	34·1 (34·1)	−23·9 (28·9)	−47·2	(30·2)
E-sel μg/ml	A	0 (4·0)	−9·7 (3·9)	−10·3	(5·4)
	P	3·9 (5·8)	5·3 (9·5)	0·4	(9·2)

There was a consistent trend to a reduction in clinical severity and serum markers of systemic inflammation (except for PMNE) in the group treated with lexipafant. Stratified analysis showed this effect to be most noticeable in the 28 cases of severe AP (APACHE II score >8). A larger study looking at clinical outcome has now started.

Acute lung injury in the microembolic model of acute pancreatitis

S W GALLOWAY, A N KINGSNORTH *(Department of Surgery, University of Liverpool)* Severe acute pancreatitis (AP) is associated with the development of an acute lung injury. The aim of this study was to discover if pulmonary injury was a feature of the microembolic model of AP in rats and to assess the therapeutic effect of a platelet activating factor (PAF) antagonist BB-882. AP was induced in 10 male Wistar rats by microembolisation of the pancreatic bed with polystyrene microspheres. After 12 hours tissue capillary permeability was assessed by an Evan's blue dye (EBD) extravasation technique and compared with control animals. A further group of rats received BB-882 30 minutes after induction of AP.

	Evan's blue dye content μg/g of wet tissue (mean (SEM))		
	Kidney	*Pancreas*	*Lung*
Control group	53·3 (1·9)	46·6 (1·7)	46·6 (1·8)
AP group	56·0 (2·1)	50·7 (1·9)	63·5 (2·6)
AP+BB-882 group	55·7 (2·1)	50·2 (1·4)	50·2 (1·4)

There was a significant increase in the tissue content of EBD in the pancreas and lungs of the group with AP (Student's *t* test $p<0·05$). BB-882 modified the pulmonary changes when given after the induction of the AP, as shown by a significant reduction in EBD content of the lungs ($p<0·01$). Increased pulmonary capillary permeability is an early feature of the microembolic model of acute pancreatitis and these changes seem to be ameliorated by administration of a PAF antagonist.

Which clinical prognostic score for acute pancreatitis? Results of a prospective multicentre study of 719 episodes

D HEATH†, D ALEXANDER, C WILSON†, M LARVIN*, C W IMRIE†, M J MCMAHON *(General Infirmary, Leeds, †Royal Infirmary, Glasgow, *Guy's Hospital, London)* Acute pancreatitis is the most unpredictable abdominal emergency, and requires prompt recognition and intervention for organ system failure (OSF) and pancreatic collections. Of the profusion of prognostic systems, only clinically based scores offer rapid assessment. The aim of the study was to evaluate systematised clinical assessment (mild: severe pain/tenderness/systemic features all absent), Ranson, Glasgow, and APACHE II scores, for the prediction of OSF and collections, defined by Atlanta criteria. During a four year period, patients admitted to 25 hospitals in Yorkshire and Glasgow with confirmed acute pancreatitis were assessed and recorded by research fellows. Of 719 episodes (382 male: 337 female, median 57 years; gall stones 36%; alcohol 24%; other causes 7%), 529 episodes were uncomplicated (74%). Of 190 severe episodes (26%), 133 patients survived (18%) and 57 died (8%).

Time	*System*	*Sensitivity*	*Specificity*	*PPV*	*NPV*	*Efficiency*
0–2 hours	Clinical	37%	96%	78%	81%	80%
	APACHE>10	70%	93%	78%	90%	87%
24 hours	Clinical	51%	96%	83%	84%	84%
	APACHE>10	76%	92%	77%	91%	88%
48 hours	Clinical	55%	96%	84%	86%	85%
	Ranson	78%	75%	50%	90%	76%
	Glasgow	86%	75%	56%	94%	78%
	APACHE>9	77%	96%	86%	92%	91%

PPV=positive predictive value, NPV=negative predictive value.

In this study population, APACHE II was confirmed as the most accurate and rapid system. Cut off scores were as formulated previously, but may be manipulated to predict trial groups of varying risk. The results strongly support the inclusion of APACHE II scores within the Atlanta criteria for severity.

Which complications of acute pancreatitis are most lethal? A prospective multicentre clinical study of 719 episodes

D HEATH†, D ALEXANDER, C WILSON†, M LARVIN*, C W IMRIE†, M J MCMAHON *(General Infirmary, Leeds, †Royal Infirmary, Glasgow, *Guy's Hospital, London)* The case mortality for acute pancreatitis remains static despite advances in intensive therapy, radiology, and surgery. Death is associated with early (<7 days), organ system failure (OSF), subsequent pancreatic collections, or both. The heterogenous nature of complications suggests that they should be studied individually, therefore we examined their incidence and relative risk utilising the Atlanta criteria. Patients with confirmed acute pancreatitis admitted to 25 hospitals in Yorkshire and Glasgow were studied prospectively, collecting clinical, investigative, operative, and necropsy data. During 48 months, 719 episodes were studied in 382 men (53%) and 337 women (47%), aged 14–97 years (median 57), caused by: gall stones 36%; alcohol 24%; other 7%. Recovery was uncomplicated in 529 attacks (74%). In 190 severe episodes (26%), 133 patients survived (18%), 57 died (8%). Early OSF occurred in 169 (24%), mortality (overall 31%) varied with multiplicity (single OSF=137, 18%; 2=26, 54%; 3=10, 90%; 4=6, 100%) and type (respiratory=148, 27%; renal=44, 64% cardiovascular=28, 93%; coagulopathy=7, 86%). Collections complicated 63 attacks (8·8%), mortality (overall 49%) varied with type (necrosis=31, 71%; pseudocysts=20, 15%; abscesses=13, 31%) and previous OSF (OSF=42, 62%; none=21, 24%). Pancreatic necrosis with increasing OSF was most lethal (single OSF=13, 62%; 2=5, 60%, 3/4=10, 100%). Of 57 deaths, 24 (42%) occurred within seven days (OSF=14; OSF+pancreatic necrosis=10), and 33 (58%) subsequently (OSF=28; OSF+collections=16; collection=5). In conclusion, although OSF complicated 92% of deaths, and collections only 54%, collections carried greater individual risk. Therapeutic emphasis should now focus on the progression from respiratory failure to multiple OSF, when mortality rises sharply, especially in the presence of pancreatic necrosis.

Dynamic contrast enhanced magnetic resonance imaging is superior to dynamic computed tomography in acute pancreatitis

M LARVIN, J WARD, P J ROBINSON, A G CHALMERS, M J MCMAHON *(The General Infirmary and St James' University Hospital, Leeds)* Dynamic, contrast enhanced computed tomography (CT) is the preferred imaging modality for acute pancreatitis. Scans are often repeated, but require large doses of toxic contrast, while regulatory authorities warn that irradiation risks are underestimated. Improvements in magnetic resonance (MR) imaging, including rapid acquisition, increased resolution, and gadopentetate dimeglumine (GdDTPA) contrast enabled us to develop an analogous technique, and to compare dynamic CT and MR imaging prospectively. Axial/coronal T2 weighted spin echo and gradient echo, 'turbo' fast low angle shot (FLASH) MR sequence were acquired (Siemens Magnetom, 1·0 Tesla) in one breathhold, before and after 0·1 mmol/kg GdDTPA by intravenous bolus. CT was performed (IGE CT-9800/Siemens Somatom+S) with oral contrast, repeated dynamically during 10–12 breathholds, after 1·5 ml/kg intravenous iopamids 370 at 2 ml/s. Scans were scored 'blindly' for viability, collection content, extrapancreatic signs, and aetiology. In 32 patients (18 male/14 female; median 53 years; gall stones=19; alcohol=5) with severe attacks (Atlanta criteria), MR and CT were comparable for pancreatic viability and vascular occlusions. MR was superior for extrapancreatic signs, collection contents, and gall stones (CT 10/9; MR 19/19). Dynamic MR imaging should be considered a frontline imaging technique for acute pancreatitis, offering advantages of more rapid scanning, no irradiation, low volume non-toxic contrast, and better characterisation of fluid collections.

Pancreatic carcinoma: an audit of treatment, survival, and quality of life

C WILSON, M E C VAN WYK, I FUNNELL, J E J KRIGE, P C BORMAN, J TERBLANCHE *(Surgical Gastroenterology, Department of Surgery, Groot Schur Hospital and University of Cape Town)* Since 1989 data has been collected prospectively on all patients presenting with pancreatic carcinoma. There were 213 patients recorded, 108 men: 105 women, median age 64 (range 28–89 years). Jaundice was the presenting complaint in 155 patients (73%). The initial treatment was surgical in 76 patients (37%) (bypass – 63, resection – 10, laparotomy – 3), endoscopic stent placement in 64 (30%), and percutaneous stent placement in 16 (7·5%). The remaining 57 patients had no palliative procedure performed. Thirteen patients had additional radiotherapy or chemotherapy, or both.

At the time of analysis 165 (77%) had died, 34 (16%) were alive, and the outcome in 14 patients was unknown. Median survivals were: resection 487 days, bypass 144 days, stent placement 127 days, and no procedure 36 days. The total time spent in hospital was significantly shorter when palliation was by stent placement rather than bypass surgery (median 16·5 *v* 21 days, p=0·009), this difference being most noticeable for those having endoscopic stent placement and surviving for periods up to six months (median 12 *v* 23 days, p=0·0002).

Quality of life was assessed by sequential ECOG scores in 70 patients and showed good preservation of performance, usually until the last month of life. Their requirement for narcotic analgesia increased, particularly during the last two months of life.

Palliation of jaundiced patients by stent placement seems to minimise the total time spent in hospital. Quality of life seems to be maintained in most patients receiving palliative treatment until shortly before death.

Results of purse string pancreaticojejunostomy after partial pancreatectomy

J G WILLIAMS, S R BRAMHALL, J P NEOPTOLEMOS *(Academic Department of Surgery, City Hospital NHS Trust, Birmingham)* Morbidity and mortality after pancreatic resection has fallen steadily. However, leakage from pancreaticojejunal anastomoses remains a significant cause of death after partial pancreatectomy. A novel technique of purse string pancreaticojejunal anastomosis is described. Seventy one patients underwent pancreatic resection between 1987 and 1994. There was no mortality within 30 days of surgery. However, three patients (with cancer) died at 31, 57, and 69 days of myocardial infarction, stroke, and sepsis, respectively. An uncomplicated recovery was made by 24 of 36 patients (66%) with cancer and 32 of 35 patients (91%) with chronic pancreatitis. In 44 patients, anastomosis between the pancreatic remnant and jejunum was performed. Twenty nine (18 cancer, 11 chronic pancreatitis) of these by end to side, sutured pancreaticojejunostomy, and the remaining 16 anastomosis (12 cancer, 4 chronic pancreatitis) were performed by a new technique of end to end purse string pancreaticojejunostomy. Three major and one minor pancreatic leaks occurred after end to side pancreaticojejunostomy, and one minor leak occurred after purse string pancreaticojejunal anastomosis. Hospital stay was shorter in patients who had a purse string anastomosis; median 11 days (range 8–23) versus 16 days (10–72; p=<0·001). The purse string pancreaticojejunostomy is quicker and easier to perform than conventional pancreaticojejunostomy and may be associated with a quicker recovery.

Tissue factor and tissue factor pathway inhibitor in human pancreatic carcinoma

A K KAKKAR, N R LEMOINE, R C N WILLIAMS *(Department of Surgery and ICRF Oncology Unit, Hammersmith Hospital, London)* Human pancreatic carcinoma is associated with a high incidence of thrombotic complications, and thrombin generation may facilitate tumour invasion and metastasis. The nature of the procoagulant and, in particular the role of tissue factor (TF) and its physiological inhibitor tissue factor pathway inhibitor (TFPI) have not been defined. Specimens of normal human pancreas (n=18) and pancreatic adenocarcinoma (n=53) were studied immunohistochemically for TF and TFPI expression using rabbit polyclonal antihuman TF and antihuman TFPI antibodies. Tumour specimens were assessed by two observers for TF expression and were graded independently for histological differentiation. Normal pancreas did not stain positively for TF or TFPI. Heavy TF staining (++/+++) was seen in three of 15 (20%) well differentiated, nine of 18 (50%) moderately differentiated, and 17 of 22 (77%) poorly differentiated tumours. The effect of tumour differentiation on TF expression was highly significant as analysed by the χ^2 test for linear trend (χ^2=6·67, p=0·0098). There was no heavy straining for TFPI, but 17 of 24 tumours stained lightly for TFPI. There was no relation with tumour grade.

The strong expression of TF may explain the hypercoaguable state in pancreatic cancer. The weak expression of TFPI may be insufficient to inhibit the strong procoagulant stimulus of TF.

PBMC regulation of the hepatic acute phase response (APPR) in cancer patients occurs via an IL-6 dependent mechanism

J S FALCONER, M G O'RIORDAIN, J P MAINGAY, M FAROUK, J A ROSS, D C CARTER, K C H FEARON *(University Department of Surgery, Royal Infirmary, Edinburgh)* The hepatic APPR is associated with increased energy expenditure in cancer patients and may contribute to cancer cachexia. In this study we investigated the hypothesis that the APPR is regulated by peripheral blood mononuclear cells (PBMC) via an IL-6 dependent mechanism. Pancreatic cancer patients (n=32) were subdivided on the basis of serum C reactive protein as a measure of the presence of an APPR. PBMC were isolated and the supernatants from 24 hour cultures added to culture of isolated human hepatocytes in the presence or absence of neutralising antibody to IL-6. Hepatocyte C reactive protein production was measured by ELISA.

In patients with an APPR both serum and PBMC IL-6 were increased. PBMC supernatants induced an APPR in cultured human hepatocytes, which was abolished by antibody to IL-6. Therapeutic strategies that modulate PBMC activation and IL-6 production may control the generation of the APPR and thereby abrogate cancer cachexia.

	Healthy control	*Cancer (no APPR)*	*Cancer (APPR)*
Subjects (n)	6	16	16
Serum CRP (mg/l)	<10	<10	73±13*†
Serum IL-6 (ng/ml)	<75	95±8*	159±38*†
PBMC IL-6 (ng/ml)	1·4±0·7	4·5±1·1*	13±1·9*†
Hepatocyte CRP (ng/ml)			
PBMC supernatants	64±20	154±26*	243±1·9*†
PBMC supernatants+ anti-IL-6	30±4	31±3‡	34±5‡

*p<0·05 *v* healthy controls, †p<0·05 *v* cancer no APPR (*t* test), ‡p<0·05 *v* supernatants without anti-IL-6 (paired *t* test).

The acute phase response and survival in pancreatic cancer

J S FALCONER, K C H FEARON, J A ROSS, R ELTON, S J WIGMORE, D C CARTER *(University Department of Surgery, Royal Infirmary, Edinburgh)* Pancreatic cancer patients have among the highest incidence of cachexia and lowest survival rates of any group of cancer patients. The aim of this study was to find out if certain metabolic and nutritional indices related to the acute phase response (APR) are prognostic factors independent of stage of disease. The variables at the time of diagnosis of 102 patients with unresectable pancreatic cancer were entered into a Cox's proportional hazards model. Included in the analysis were serum C reactive protein (CRP) and albumin, weight loss, age, sex, and stage of disease (UICC). The median survival of those with an APR (CRP >10 mg/l; n=45) was 66 days compared with 222 days in those without an APR (n=57; p=0·0001, Mann-Whitney U). The results of multivariate analysis in which each factor has been adjusted for the influence of other factors are shown in the Table. Factors for inclusion in this model were identified by a preliminary univariate analysis.

Variable	*p Value*
Serum CRP	<0·0001
Serum albumin	0·0001
Stage of disease	0·0036
Age	0·0183

The presence of an APR was the most significant predictor of survival and this was independent of stage of disease. These findings suggest that the metabolic disturbances that occur in association with the APR in pancreatic cancer may be a worthwhile therapeutic target.

Ibuprofen versus placebo in the treatment of pancreatic cancer cachexia

S J WIGMORE, J S FALCONER, J A ROSS, C E PLESTER, J P MAINGAY, D C CARTER, K C H FEARON *(University Department of Surgery, Royal Infirmary, Edinburgh)* Profound weight loss is commonly associated with pancreatic cancer. Cachexia has been linked with increased resting energy expenditure (REE) and activation of the hepatic acute phase response (APPR). These effects are thought to be mediated by IL-6 through direct or prostaglandin mediated pathways.

Sixteen patients with histologically confirmed carcinoma of the pancreas under-

went nutritional assessment and serum sampling before and after treatment with 1200 mg per day for seven days of the cyclooxygenase inhibitor ibuprofen. REE was measured by indirect calorimetry (Deltatrac Analyser).

Measurement of REE was higher than predicted values in all patients but was reduced after treatment with ibuprofen (n=10) compared with placebo (n=6). Reduction in REE was paralleled by reduction in serum C reactive protein concentration in the ibuprofen group.

	Before ibuprofen	*After ibuprofen*	*Two tailed t test*
REE total KCal (SEM)	1468 (98·6)	1386 (88·9)	p<0·02
CRP mg/l^{-1} (mean)	484·2 (143·5)	254·2 (82·9)	p<0·05

These results show that ibuprofen may have a significant benefit in reducing REE and acute phase protein production in patients with pancreatic cancer. Further studies are required to discover if these changes correlate with reduction in weight loss in patients with cachexia.

Pancreatic cancer cell derived IL-8 stimulates hepatic acute phase protein production in vitro and serum IL-8 correlates with serum CRP in pancreatic cancer patients in vivo

S J WIGMORE, J A ROSS, K C H FEARON, J S FALCONER, J P MALNGAY, D C CARTER *(University Department of Surgery, Royal Infirmary, Edinburgh)* The hepatic acute phase protein response is an important component of the catabolic processes that contribute to weight loss in pancreatic cancer. We show that both recombinant human IL-8 and tumour cell derived IL-8 stimulated acute phase protein production in isolated human hepatocytes. Addition of recombinant human IL-8 or pancreatic cancer cell supernatants resulted in the following changes in CRP production.

	rec Hu IL-8	*MiaPa Ca-2*	*CFPAC*	*PANC1*
Time 48	10 ng/ml 160	CRP ng/ml 350	CRP ng/ml 240	CRP ng/ml 70

Stimulation of CRP production by human pancreatic cancer cell supernatants could be inhibited by the addition of neutralising antibodies as follows:

	% Inhibition		
Antibody	*MiaPa Ca-2*	*CFPAC*	*PANC1*
Anti-h IL-8	113	0	50
Anti-h IL-6	7	78	0

Furthermore, we show that serum IL-8 correlates with the presence of an acute phase protein response in 63 patients with pancreatic cancer (r=0·68, p=0·0001). Tumour cell derived IL-8 may have a role in the aetiology of the acute phase response in cancer cachexia.