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Prognostic markers in acute pancreatitis: can pancreatic necrosis be predicted?

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Summary

The value of six prognostic markers was assessed prospectively in 198 attacks of acute pancreatitis with specific attention to their ability to predict pancreatic necrosis. The Imrie Prognostic Score (IPS) was recorded within 48 h of diagnosis. The serum C-reactive protein (CRP) α_1 antiprotease (A1AP), α_2 macroglobulin (A2M), amylase and white cell count (WCC) were measured on days 1, 3 and 7.

When comparing all severe clinical outcomes to mild outcomes, serum CRP concentrations were higher on all three days ($P<0.02$, <0.001, <0.001), A1AP concentrations were higher on day 3 ($P<0.05$), A2M concentrations were lower on day 7 ($P<0.01$) and WCC was higher on all three days ($P<0.001$, <0.001, <0.001). Serum amylase concentrations showed no significant differences. None of the measured parameters were helpful in distinguishing patients who subsequently developed pancreatic necrosis from patients who had other severe outcomes.

Multivariate analysis revealed that the initial IPS showed greatest independent significance in predicting severe outcome followed by the WCC (days 1 and 7) and CRP (day 3).

CRP and WCC may be clinically useful predictors of severe outcome to supplement the initial IPS. These methods are unlikely to distinguish pancreatic necrosis from other severe outcomes, but they may supplement clinical judgement in selecting a high risk group of patients for contrast enhanced computed tomography.

Introduction

Of patients with acute pancreatitis 20% develop major complications, from which approximately half will die with conventional treatment alone. Even severe cases can be cured by medical therapy if the pancreatic disease is restricted to interstitial inflammation. Necrotising pancreatitis, however, holds a high risk of local infection and generalised sepsis leading to toxic organ complications. This can be avoided by the surgical removal of necrotic tissue, but this poses the problem of identifying patients with significant pancreatic necrosis in time for successful surgery. If surgery is delayed until complications are established, the postoperative mortality is prohibitive.

Contrast enhanced computed tomography (CT) has enabled the early identification of pancreatic necrosis as areas of decreased enhancement within the gland *(1–4)*. A policy of early surgery for extensive pancreatic necrosis demonstrated by this technique has resulted in acceptably low postoperative mortality (6.5%) in a specialist centre in West Germany *(4)*. CT for all patients with acute pancreatitis is expensive, particularly when serial investigations are performed. Preliminary selection of patients at high risk is required.

Areas of necrosis form fairly early in the attack of acute pancreatitis. It is likely that inflammation around the necrotic focus exists throughout the period of evaluation. It is thus reasonable to screen for occult necrosis using plasma indicators of the inflammatory response such as 'acute phase proteins' (C-reactive protein and α_1 antiprotease) and the white cell count. Serum amylase may be of value as it is reported to remain elevated in some patients who develop pancreatic collections *(5)*. Conventional multifactor prognostic scoring systems *(6,7)* and the consumptive depletion of α_2 macroglobulin *(8–10)*, the most important serum antiprotease, can also be used to predict severe outcome.

Recently the combined determination of the serum concentrations of C-reactive protein (CRP) and α_2 macroglobin (A2M) has been recommended to stage the severity of disease *(11)*. The reported necrosis detection rates for CRP (95%) and A2M (85%) compared favourably to that of contrast enhanced CT (90%) and it was suggested that they might replace this investigation.

Clearly this would have major financial and therapeutic implications. This study was designed to further evaluate serial CRP and A2M measurement in predic-

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TABLE I *Imrie prognostic criteria used to predict severity of attack of acute pancreatitis (6)*

Age	>55 years
WCC	$>15\times10^9$/l
Urea	>16 mmol/l
Glucose	>10 mmol/l
Albumin	<32 g/l
Calcium	<2.0 mmol/l
Pa_{O_2}	<8 kPa
ALT	>100 IU/l
LDH	>600 IU/l

Predicted mild attack 0–2 factors
Predicted severe attack 3–9 factors

tion of outcome in acute pancreatitis and the development of pancreatic necrosis in particular. Their prognostic value is compared with the initial Imrie Multifactor Prognostic Score *(6)* (IPS), α_1 antiprotease (A1AP), amylase and white cell count (WCC).

Patients and methods

From February 1985 to April 1987 patients admitted to hospitals in and around Leicester with a clinical picture compatible with acute pancreatitis and serum amylase greater than 1000 IU/l were included in the study.

The original nine Imrie prognostic criteria *(6)* (Table I) were recorded as soon as possible after diagnosis and in all cases within 48 h to provide a prognostic score (IPS). Blood was taken on days 1, 3 and 7 for measurement of CRP, A1AP, A2M, amylase and WCC. The patient's clinical progress was followed. A severe outcome was defined as death, a major complication or a hospital stay in excess of 20 days, excluding social problems and elective biliary surgery as reasons for prolonging the admission.

Pancreatic necrosis was confirmed at laparotomy or postmortem examination as macroscopic areas of devitalised tissue with or without an associated collection of pus (abscess). Pseudocysts were only included as major complications if they persisted after 6 weeks or required early drainage because of complications. Small collections of fluid in or around the pancreas detected by CT or ultrasound examination during the course of the disease, but which did not persist, were not regarded as severe outcomes. Pseudocysts were only included with the necrotic complications if they were associated with devitalised tissue requiring surgical excision.

During the course of this study CT scan was performed on a minority of patients with low volume contrast enhancement only. The scans were not performed with high volume contrast enhancement nor with the quality of machine and expert radiological opinion available in Ulm *(4,11)*. The quality of the scans was inadequate to detect pancreatic necrosis and no patient was subjected to 'early' surgery for resection of pancreatic necrosis detected on CT scan. When laparotomy was performed it was because of continued deterioration in patients with multi-organ failure despite intensive medical therapy. This 'late' surgery was usually performed in the second or third week of the illness and involved sequestrectomy and abscess drainage where indicated in an attempt to halt the downward trend in the patient's condition.

Serum CRP was measured by single radial immunodiffusion *(12)* using preformed gels (LC-Partigen-CRP, OTDO 02/03, Hoechst-Behring, Marburg, W. Germany). Serum A1AP and A2M were measured using goat antiserum and Calibrator-1 (Atlantic Antibodies Ltd) on a Cobas Bio centrifugal analyser on turbidimetric mode. Reference ranges were established using data from a sample of healthy adults selected randomly from the general population in and around Leicester.

STATISTICAL METHODS

Analyses between days for the prognostic factors were carried out using the non-parametric Friedman two-way analysis of variance for three matched samples *(13)* and by the Wilcoxon matched pairs signed ranks test. Between outcome group comparisons were achieved by means of the Kruskal–Wallis *(14)* one-way analysis of variance and by the Wilcoxon rank sum test.

Multivariate analysis was by stepwise logistic regression *(15)*.

Results

One hundred and ninety-eight attacks of acute pancreatitis were studied in 164 patients. The median age of the patients was 59 years (range 13–91) and 52% were female. The aetiology of the attacks was gallstones in 57%, alcohol in 21%, other aetiologies in 8% and idiopathic in 14%.

Thirty-eight attacks (19.2%) resulted in a severe clinical outcome with 17 deaths (8.6%). Twenty patients (10.1%) developed pancreatic necrosis confirmed at laparotomy or postmortem examination. Three patients developed pseudocysts which were drained percutaneously (2) or surgically (1).

Seventy-two attacks were predicted severe on the initial Imrie prognostic score of which 30 (41.7%) had a severe outcome with 16 deaths (22.2%) and 14 patients with pancreatic necrosis (19.4%). Of the 126 attacks predicted as mild, eight (6.3%) had a severe outcome with one death (0.8%) and six patients with pancreatic necrosis (4.8%). The prognostic score was significantly higher in patients with severe outcome (median 4, range 1–7) than in patients with mild outcome (median 2, range 0–7, $P<0.01$)). The sensitivity of the prognostic scoring system was 79% and the specificity 74%. The predictive value of a score of three or greater was 41.7% and the predictive value of a negative score (less than three) was 93.7%.

Looking at the parameters measured on days 1, 3 and 7, Table II gives the medians and ranges for the variables on each of the three recording occasions. Table III gives the medians and ranges for the variables on each of the three recording occasions subdivided by outcome group.

CRP levels rose significantly from day 1 to day 3 ($P<0.001$) in the whole group of patients and by day 7 had returned towards normal ($P<0.001$). CRP levels were significantly higher on all three days in the severe outcome group compared to the mild ($P<0.02$, <0.001, <0.001) (Fig. 1*a*).

A2M levels were below the normal range on all three days and fell significantly from day 1 to day 3 ($P<0.001$) with some recovery towards normal by day 7 ($P<0.001$). A2M levels were significantly lower on day 7 in the

TABLE II *Median value of variables on each day (range)*

		CRP g/l	*A1AP* g/l	*A2M* g/l	*Amylase* IU/l	*WCC* $\times 10^9$/l
Day 1		0.056 (0–0.311)	2.0 (0.9–5.1)	1.8 (0.7–5.0)	3160 (1001–74000)	14.3 (3.3–38.3)
Day 3		0.127 (0–0.311)	2.6 (0.9–6.3)	1.6 (0.4–4.1)	555 (51–13354)	11.1 (1.4–35.5)
Day 7		0.067 (0–0.220)	2.7 (0.9–7.8)	1.8 (0.8–6.7)	250 (27–9220)	9.45 (3.6–38.2)
Overall significance by Friedman two-way analysis of variants		$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$
Pairwise comparisons by Wilcoxon matched pairs signed ranks test	1 *vs* 3	$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$
	1 *vs* 7	NS	$P<0.001$	NS	$P<0.001$	$P<0.001$
	3 *vs* 7	$P<0.001$	$P<0.01$	$P<0.001$	$P<0.001$	$P<0.001$

TABLE III *Median value of each variable on each day for each outcome group (range)*

		CRP g/l		*A1AP* g/l		*A2M* g/l		*Amylase* IU/l		*WCC* $\times 10^9$/l	
Day 1	M	0.035	(0–0.311)	1.95	(0.9–5.1)	1.8	(1.0–5.0)	3160	(1001–74000)	13.45	(3.3–28.6)
	S−N	0.104	(0–0.261)	2.1	(1.6–3.5)	1.7	(1.0–3.3)	2617	(1100–9570)	17.4	(5.6–32.0)
	S+N	0.088	(0–0.219)	2.0	(1.1–3.3)	2.0	(0.7–3.6)	3330	(1134–13600)	18.8	(9.9–38.3)
Day 3	M	0.113	(0–0.311)	2.5	(0.9–5.5)	1.6	(0.7–4.1)	517	(51–13354)	10.25	(2.4–25.1)
	S−N	0.161	(0–0.236)	2.7	(1.4–3.6)	1.65	(0.4–2.0)	401	(60–6450)	13.8	(1.4–35.5)
	S+N	0.199	(0.019–0.286)	3.0	(1.7–6.3)	1.7	(0.9–2.8)	1007	(101–3276)	14.2	(4.8–32.3)
Day 7	M	0.041	(0–0.213)	2.6	(0.9–7.0)	1.8	(0.9–6.7)	258	(27–9220)	8.9	(3.6–22.3)
	S−N	0.099	(0.002–0.189)	2.75	(2.0–3.5)	1.4	(0.8–2.0)	235	(93–1260)	10.9	(4.7–21.6)
	S+N	0.159	(0.010–0.220)	2.85	(0.9–7.8)	1.5	(0.8–2.7)	243	(88–4030)	14.7	(6.6–38.2)

M = Mild outcome
S−N = Severe outcome without pancreatic necrosis
S+N = Severe outcome with pancreatic necrosis

TABLE IV *The use of the independently significant risk factors to predict the development of pancreatic necrosis*

Risk factor	*True positives**	*False positives†*	*Sensitivity*	*Specificity*
1. Imrie Prognostic Score≥3	14/20	58/178	70%	67%
2. Day 7 WCC>15×10^9/l	11/20	13/178	55%	93%
3. Day 3 CRP>0.15 g/l	14/20	51/178	70%	71%
Scoring systems based on the above:				
1 out of 3	19/20	86/178	95%	52%
2 out of 3	13/20	31/178	65%	83%
3 out of 3	7/20	3/178	35%	98%

*True positives = patients who subsequently developed pancreatic necrosis
†False positives = patients who subsequently had a mild outcome or a severe outcome without pancreatic necrosis

severe outcome group compared to the mild ($P<0.01$) (Fig. 1*b*).

A1AP levels were elevated on day 1 and rose significantly from day one to day 3 ($P<0.001$) and from day 3 to day 7 ($P<0.01$). A1AP levels were significantly higher on day three in the severe outcome group compared to the mild ($P<0.05$) (Fig. 1*c*).

The WCC fell significantly from day 1 to day 3 ($P<0.001$) and from day 3 to day 7 ($P<0.001$) back towards normal range. The WCC was significantly higher on all three days in the severe clinical outcome group compared to the mild ($P<0.001$, <0.001, <0.001) (Fig. 1*d*).

Serum amylase levels fell significantly from day 1 to day 3 ($P<0.001$) and from day 3 to day 7 ($P<0.001$) back towards normal range. Serum amylase was of no value in separating patients with severe from mild outcomes (Fig. 1*e*).

Neither the initial Imrie prognostic score nor any of the parameters measured on days 1, 3 and 7 showed any

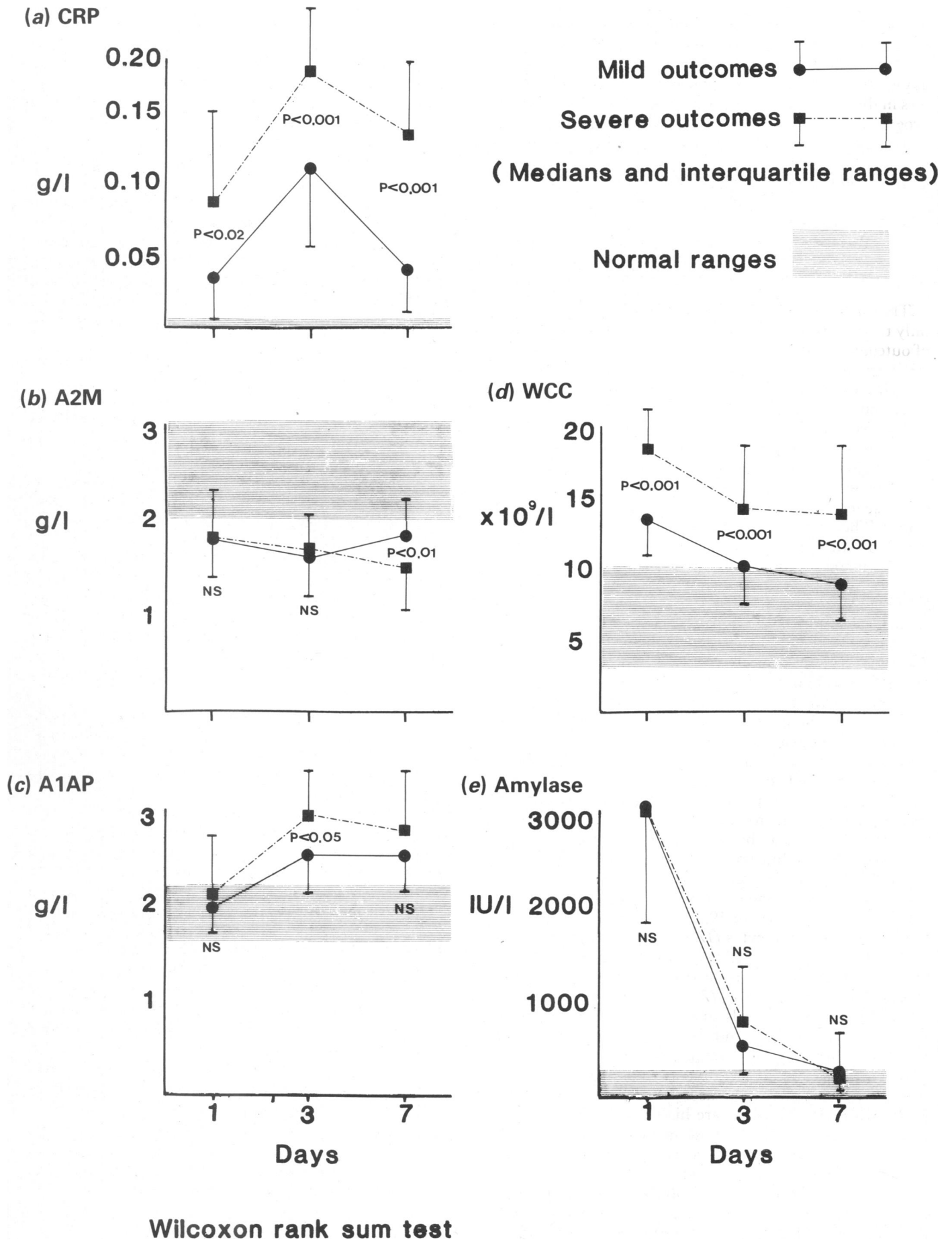

FIG. 1 Results of blood tests comparing patients with mild and severe outcomes.

significant difference between patients who subsequently developed pancreatic necrosis and those who had other severe clinical outcomes without pancreatic necrosis.

Stepwise logistic regression was carried out for each day in order to determine independently significant factors in the prediction of severe outcome. The initial Imrie prognostic score was included with the parameters measured on each day. The models obtained were as follows:

$$\text{Day}_i \text{ Probability of severe outcome} = \frac{e^{Ai}}{1+e^{1i}}$$

where i = 1, 3 or 7

$A_1 = -4.2396 + 0.62827$ (IPS) $+ 0.07055$ (WCC)

$A_3 = -4.8940 + 0.82702$ (IPS) $+ 7.3241$ (CRP)

$A_7 = -4.9089 + 0.65979$ (IPS) $+ 0.15617$ (WCC)

This indicates that the initial IPS and WCC were the only two independent significant factors in the prediction of outcome on days 1 and 7, while on day 3 the IPS and CRP are the only two independently significant factors.

Table IV depicts potentially useful methods of using these independently significant factors to select patients at high risk of developing pancreatic necrosis. It shows the predictive value of an initial IPS$\geq$3, day 7 WCC$>15\times10^9$/l and day 3 CRP>0.15 g/l in separating patients who developed necrosis from those who had other severe outcomes without necrosis or mild outcomes. The sensitivity and specificity of scoring systems based on the presence of one, two or three of these adverse factors is also given.

Discussion

At present contrast enhanced CT is the most accurate method for the early detection of pancreatic necrosis during acute pancreatitis. In this technique, precontrast upper abdominal CT is performed then a bolus of intravenous contrast is rapidly injected. The contrast enhancement of the pancreas is recorded and can be plotted on a standard curve. Enhancement is decreased significantly in patients with severe necrotising pancreatitis compared to milder forms of the disease *(1–4)*. CT is expensive and preselection of patients at highest risk of pancreatic necrosis is desirable.

CRP and A2M may be useful predictors of outcome in acute pancreatitis, but the suggestion that they can be as accurate in predicting pancreatic necrosis as contrast enhanced CT *(11)* is new and somewhat surprising.

CRP was discovered in 1930 *(16)* and is known to be synthesised by hepatocytes *(17,18)*. An increase in serum CRP concentration is well recognised as a non-specific response to a wide variety of tissue injuries *(17,19)*. Its precise role is not known *(17,18)*, but it may recognise toxic autogenous materials in the plasma released from damaged tissues to bind and detoxify them and/or facilitate their clearance *(17)*. Sequential measurements of CRP can be helpful in providing a warning of inflammatory complications in disease. In acute pancreatitis serum CRP concentrations are higher in patients with a severe outcome than in those with a mild outcome *(8,20,21)*. CRP can identify severe pancreatitis which may not be obvious at its outset *(20)*. Previous workers suggested that the main value of CRP is to provide a guide to the severity of inflammation and increase the clinician's awareness of the patient's enhanced risk of developing pancreatic necrosis. CRP was not able to differentiate attacks which were severe because necrosis developed from those that were severe for other reasons *(20)*. CRP may be superior for selecting patients at risk from pancreatic necrosis than the WCC, erythrocyte sedimentation rate, AlAP, antichymotrypsin, and the patient's temperature *(20)* or Ransons Multifactor Prognostic Score *(21)*. Thresholds of 0.1 g/l *(20)* and 0.11 g/l *(21)* have been suggested for CRP, above which the patient's risk of developing pancreatic necrosis is greatest. We have found a threshold of 0.15 g/l to be more useful.

Radial immunodiffusion was used to measure CRP in this study due to cost considerations and the non-urgent nature of the specimens. Results were therefore not available for at least 48 h. Other methods for automated CRP measurement including radioimmunoassay and nephelometry are available to give results in less than 1 h if clinical decisions are to be based on the measurement *(17,18,22)*.

A2M is a large molecular weight antiprotease which occupies a central role in the elimination of enzymes released from the gland during acute pancreatitis. It binds enzymes in a unique reaction involving a conformational change in the molecule *(23)*. The resulting complexes are then taken up and destroyed by the reticuloendothelial system, particularly the Kupffer cells of the liver *(24)*. The consumptive depletion of serum A2M correlates with the severity of outcome in acute pancreatitis *(8–10)*.

This study confirms that serum CRP levels are significantly higher in patients with severe disease (days 1, 3 and 7) compared to those with mild disease and that A2M levels are lower in severe disease (day 7) than in mild. It has also demonstrated that WCC (days 1, 3 and 7) and A1AP concentrations (day 3) are higher in severe outcomes compared to mild. Serum amylase was unhelpful in predicting severity of outcome.

None of the measured parameters was able to distinguish patients who subsequently developed pancreatic necrosis from those who had other severe outcomes, though the number of patients in each category was relatively small.

Multivariate analysis suggested that none of the measured parameters was more useful than the initial Multifactor Prognostic Score (IPS) in predicting severity of outcome. However, subsequent WCC (day 7) and CRP (day 3) may be of value in selecting patients for contrast enhanced CT. None of the prognostic markers is accurate enough to replace contrast enhanced CT in selecting patients with pancreatic necrosis for early surgery.

If a policy of early surgery for patients with extensive pancreatic necrosis is to be adopted then contrast enhanced CT is justifiable. Preselection of patients for CT can be made on the basis of an initial IPS$\geq$3 or a day 3 CRP>0.15 g/l or WCC$>15\times10^9$/l at 1 week. If clinical judgement is used to augment this selection process then it is unlikely that patients with significant pancreatic necrosis will be overlooked.

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Notes on books

Rhinoplasty: emphasising the external approach by Jack R Anderson and W Russell Ries. 177 pages, illustrated. Georg Thieme Verlag, New York. DM 98.

Rhinoplasty performed for reconstruction of a damaged nose has been an operation performed for many centuries. Rhinoplasty for purely aesthetic purposes, however, is an operation of relatively recent origin. This large format glossy monograph relates to the operation performed for cosmetic indications and is written by two authors who have performed an estimated seven to eight thousand such operations between them. The lessons learned from this vast experience are here passed on to others.

Cancer Chemotherapy by Infusion edited by Jacob J Lokich. 747 pages, illustrated. MTP Press Limited, Chicago. £80.

A comprehensive review of the present state of treating various cancers by infusion chemotherapy. Most of the authors are from the United States. Section one is on the rationale and technical aspects. Then follows sections on the various therapeutic agents and the treatment of various tumours by systemic infusion. The fourth section is on techniques of regional infusion. A reference volume for surgical oncologists.

Mastery of Surgery edited by Lloyd M Nyhus and Robert J Baker. 1540 pages, illustrated. One volume international edition. Little, Brown, Boston. £45.

This book was first issued in 1984 in two volumes at a price in the United Kingdom of £182. It was given a complimentary full review in the Annals in July 1985. It has now been issued at a substantially reduced price as a single volume and, as such, should be of considerable interest to all who wish to have a comprehensive and first-rate manual of operative surgery on their shelves. Well illustrated, easy to read, adequately referenced and strongly recommended.

Dental Oral and Maxillofacial Surgery: a Guide to Hospital Practice by David Poswillo, Alex Babajews, Malcolm Bailey and Murray Foster. 224 pages, paperback, illustrated. William Heinemann Medical Books, London. £9.95.

A book for the white coat pocket of senior dental students, house officers and general dental practitioners who seek a concise account; in short note form, of the principles of dental, oral and maxillofacial surgery. Sensibly priced, sturdily bound, this book should sell well.