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C-reactive protein (CRP) and serum phospholipase A_2 in the assessment of the severity of acute pancreatitis

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SUMMARY The present study examines the value of C-reactive protein (CRP) determinations in the assessment of the severity of acute pancreatitis and the correlation of CRP with serum phospholipase A_2 activity and the clinical status. Fifty three patients with acute pancreatitis were studied; 17 with haemorrhagic pancreatitis and 36 with a mild form of the disease. S-phospholipase A_2 activity increased significantly ($p<0.05$) in patients with fatal pancreatitis but not in those with mild disease. Phospholipase A_2 concentrations were below 10 nmol FFA/ml min in mild, while they rose to 20–40 nmol FFA/ml min in haemorrhagic pancreatitis. In fatal cases very high (up to 50–60 nmol FFA/ml min) serum phospholipase A_2 concentrations were recorded. The increase in CRP was greater in the patients with severe pancreatitis. One day after admission mean CRP was 280 mg/l in patients with haemorrhagic and 45 mg/l in those with the mild pancreatitis ($p<0.001$). High CRP values also correlated with the prognostic signs indicative of severe pancreatitis. CRP and S-phospholipase A_2 determinations are valuable in the early assessment of the severity of acute pancreatitis, but the CRP assay is much easier to include in hospital routine.

Acute pancreatitis varies from a mild, spontaneously healing condition to a severe disease with damage to remote organs and a high mortality rate – up to 80%.[1,2] One of the main problems in treating patients with pancreatitis has been the lack of reliable methods for detecting haemorrhagic pancreatitis in the early stages[3,4] and this has often led to delay in giving vital adequate treatment.[3,4]

Phospholipase A_2 is an enzyme known to play an important role in the pathogenesis of acute pancreatitis.[5,6] It is produced in the pancreas, where it is normally present as the inactive precursor, prophospholipase A_2, which is activated to phospholipase A_2 by trypsin and other proteolytic enzymes when secreted into the duodenum.[5,7] Phospholipase A_2 converts the lecithin and cephalin in cell membranes and bile into their cytotoxic lysocompounds.[5,8] Owing to their detergent like properties, these lysocompounds tend to cause pancreatic necrosis and the various severe systemic complications seen in acute pancreatitis.[5,9] In both human and experimental pancreatitis,[6,8,10] phospholipase A_2 has raised activity, which correlates well with the pulmonary changes and the severity of the acute pancreatitis.[10]

C-reactive protein was discovered in 1930 by Tillett and Francis.[11] These workers were investigating serologic reactions in pneumonia with various extracts of pneumococci and observed that a non-type-specific somatic polysaccharide fraction, which they designated fraction C, was precipitated by the sera of acutely ill patients.[11] C-reactive protein is known to be synthesised by hepatocytes.[9,12,13] The precise role of CRP *in vivo* is not known.[9,13] One theory suggests that the main role of CRP is to recognise the potentially toxic autogenous materials in the plasma released from damaged tissues, to bind and detoxify them and/or facilitate their clearance.[13] Methods currently available for detection and quantification of CRP are radial immunodiffusion, electroimmunodiffusion, radioimmunoassay, nephelometry, enzyme labelled immunoassay and fluoroimmunoassay.[9,14,15] The clinical measurement of CRP is valuable as a screening test for organic disease and as a sensitive

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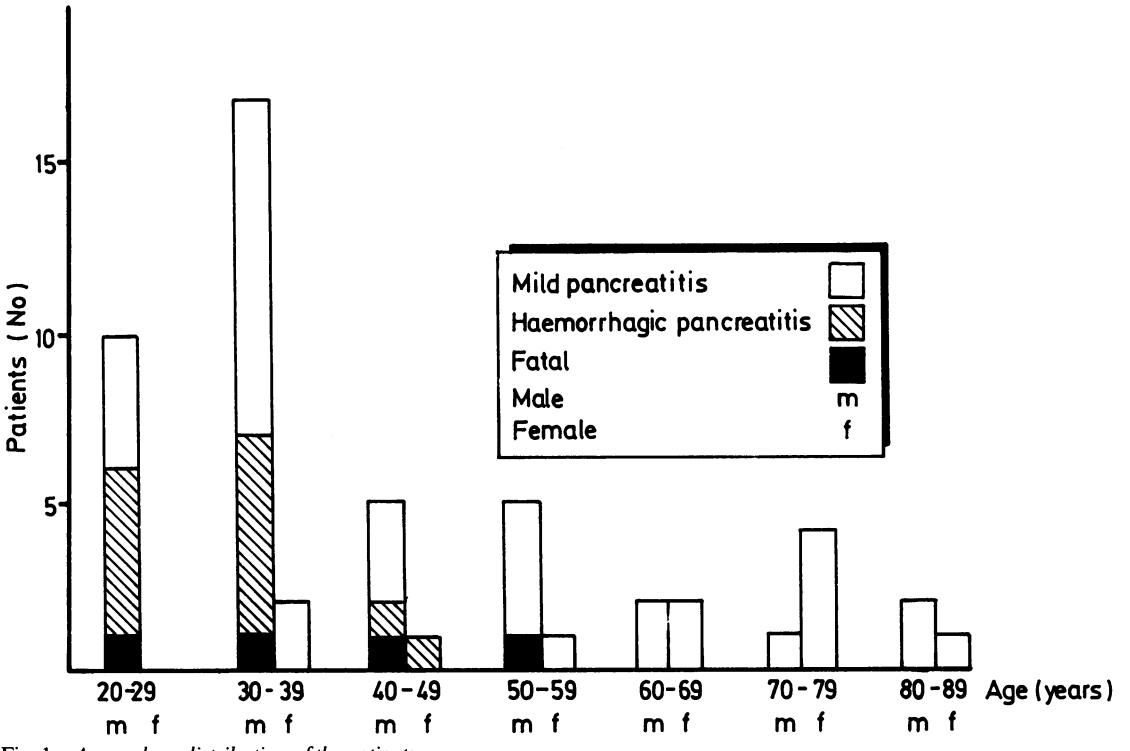

Fig. 1 *Age and sex distribution of the patients.*

objective index of disease activity and response to therapy in some inflammatory, infective and ischaemic conditions.[9 12 13 15]

The present study was done to assess the value of CRP determinations in acute pancreatitis and to ascertain whether the CRP values correlate with the serum phospholipase A_2 activity and the clinical situation.

Methods

PATIENTS

Fifty three patients with acute severe pancreatitis were included in this prospective study. The patients were admitted to Helsinki University Central Hospital in 1983-4. The patients were considered to have severe symptoms on admission and they were consecutive. The diagnosis was usually based on raised urine amylase levels and clinical symptoms of the patients. There were 42 (79%) men, mean age 41 years (range 24–86) and 11 (21%) women, mean age 62 years (range 30–86) (Fig. 1).

The aetiology of acute pancreatitis in these patients is presented in Table 1. Alcohol was the aetiologic factor in 94% of patients with haemorrhagic pancreatitis. For the whole series this figure was 70%. Biliary tract disease caused pancreatitis in 40% of patients with the mild form of the disease and in 21% of all patients. In men the main aetiologic factor was alcohol (79%), whereas in women most of the episodes seen were caused by biliary tract disease (55%). Postoperative status was responsible for the pancreatitis in one case. The diagnosis was based on the clinical symptoms and the rise in serum and urine amylase (U-amyl 36 890 and S-amyl 6920) values. In four cases the aetiology of the disease remained unknown. Thirty two (60%) patients were having their first attack of acute pancreatitis. This group included all four patients with fatal pancreatitis. Only three of 17 patients with haemorrhagic pancreatitis were having a recurrence of the illness. Among the

Table 1 *Aetiology of the pancreatitis*

	Haemorrhagic pancreatitis	*Mild pancreatitis*	*Total*
Alcohol	16	21	37 (70%)
Biliary disease	1	10	11 (21%)
Postoperative state	–	1	1 (2%)
Unknown	–	4	4 (8%)
Total			53

patients with mild pancreatitis first episodes were as frequent as recurrences. The numbers of attacks of pancreatitis are presented in Table 2.

The patients were divided into three groups for analysis:

Group 1: Four patients who died of acute haemorrhagic pancreatitis. These were men and mean age in this group was 40 years (range 24–59 years). Diagnoses were verified at laparotomy.

Group 2: Thirteen patients with acute haemorrhagic pancreatitis who survived; 12 men and one woman. Mean age was 32 years (range 26–46 years). Diagnosis was also verified at laparotomy.

Group 3: 36 patients with mild pancreatitis. Thirty five of whom recovered without complications and in one case a pancreatic pseudocyst developed. This group consisted of 26 men (mean age 45 years; range 26–89 years) and 10 women (mean age 64 years; range 30–86 years).

TREATMENT (TABLE 3)

Patients with a fulminant course of the disease with symptoms of respiratory failure, shock and/or peritonitis were suspected of severe disease and underwent laparotomy. Many of these patients had decreased contrast enhancement in computed tomography as reported elsewhere[16] and many of them are included in a prospective randomised study comparing peritoneal lavage and pancreatic resection for haemorrhagic pancreatitis.[17] The diagnosis was verified by microscopy in the cases with resection and by inspection in the cases with operative peritoneal lavage.[17] Six (35%) of the 17 patients with haemorrhagic pancreatitis had subtotal resection as the primary treatment. Nine patients (53%) with haemorrhagic pancreatitis were treated preoperatively by peritoneal lavage. They were included in a randomised study in the clinic. In two patients (12%) with severe pancreatitis the primary treatment with peritoneal lavage was later followed by subtotal pancreatic resection because of rapid deterioration in their condition. Twenty-nine (81%) of the 36 patients with mild pancreatitis recovered after conservative treatment. One patient had to be operated on because of a complication; canalisation of a pancreatic pseudocyst was followed by pancreatic resection. The remaining six patients in this group were operated on after primary conservative treatment for biliary disease.

Table 2 *Episodes of pancreatitis (n)*

	Haemorrhagic pancreatitis	*Mild pancreatitis*	*Total*
First attack	14	18	32
Recurrence	3	18	21
Total	17	36	53

DURATION OF HOSPITAL TREATMENT

The mean duration of the hospital treatment for the series as a whole was 17 days (±SD 15 days). For the patients with haemorrhagic pancreatitis this figure was 29 days (±SD 20 days), and for those with mild disease 11 days (±SD seven days).

LABORATORY TESTS

Blood samples were taken daily for a week in mild cases and for two weeks in patients with severe pancreatitis or a complicated course of the disease. Samples were taken to determine the prognostic signs of Ranson,[18] modified according to our hospital routine.

PHOSPHOLIPASE A_2

The serum phospholipase A_2 assay was carried out by a recently developed method.[19] For determination of serum phospholipase A_2 activity, L-3-phosphatidylcholine,1-palmitoyl-2-9,10(n)-^{3}H palmitoyl (98% pure by thin layer chromatography) with a specific activity of 35 Ci/mmol was purchased from Amersham International, Bucks, England. The corresponding non-radioactive lipid was from Sigma Chemical Co, No. P-0763, St Louis, Mo, USA. The assay of phospholipase A_2 activity was based on hydrolysis of a sonicated emulsion of 2-palmitoyl-9,10(n)-^{3}H-labelled dipalmitoylphosphatidylcholine and assay of free palmitic acid radioactivity. For this purpose 16·125 mg DPPC and 40 μCi of 2-9·10(n)^{3}H palmitoyl-labelled DPPC were dried under nitrogen. After addition of 2·2 ml of 50 mM TRIS-HCL buffer,

Table 3 *Treatment of the patients*

	Pancreatic resection	*Operative peritoneal lavage*	*Peritoneal lavage+late resection*	*Conservative*	*Conservative+late operation*	*Total*
Group I	1	1	2	–	–	4
Group II	5	8	–	–	–	13
Group III	–	–	–	29	7	36
Total						53

pH 7·4, containing 20 mM cholate and 10 mM CaCl, the solution was sonicated with a Branson sonifier cell disrupter type 15 B (Branson Inc, Danbury, CT, USA). The enzyme preparations, with 40 µl substrate emulsion and a sufficient quantity of 0·9% (W/V) NaCl to make up the final volume to 100 µl, were placed in glass tubes which were then vortexed vigorously and incubated for 20 min at 37°C. The final concentration of DPPC in the assay was thus 4 mM. The reaction was terminated by adding 3·25 ml of chloroform-methanol-heptane (1·41;1·25;1·0 V/V). This was followed by 0·75 ml of 0·14 M borate buffer (pH 10·5) and 0·4 ml water. The tubes were then mixed on a Vortex mixer and centrifuged for 40 min at 2600 *g*. From the upper phase containing the radioactive free fatty acids (FFA) 1·8 ml was counted for radioactivity in a Wallac Rack Beta liquid scintillation counter, using 10 ml ACS^R, Amersham International, Bucks, England. The radioactivity detected in the FFA fraction was used to calculate the amount of FFA released during incubation. Phospholipase A_2 activity is expressed as nmoles of FFA released per minute per millilitre of serum (nmol FFA/min ml).

CRP

Samples for CRP determination were also taken daily. The CRP determinations were made with the Emit^R C-reactive protein assay (Syva CO, USA). The Emit^R assay is a homogenous enzyme immunoassay technique in which the serum sample is mixed with two reagents: reagent A contains antibodies to CRP and substrate for the enzyme B-D-galactosidase; reagent B contains CRP-enzyme conjugate. Reagent A is added to the sample first, and the antibody binds to CRP. After an equilibrium period Reagent B is added and the CRP-enzyme conjugate binds to any remaining antibodies; this binding excludes the enzyme's substrate. Some enzyme conjugate remains unbound and therefore continues active in the reaction mixture. The active enzyme cleaves the substrate, producing an absorbance change that can be measured spectrophotometrically. This enzyme activity is directly related to the concentration of CRP present in the sample. The normal range for CRP concentrations in healthy adults is below 10 mg/l.[9 15 20]

STATISTICAL ANALYSIS

Analysis of variance followed by Student's *t* test was used to calculate significances of differences between the groups.

Results

PROGNOSTIC SIGNS

The prognostic signs were calculated for all patients. Age, white blood cell count, serum calcium, serum protein, serum creatinine, SGOT as well as arterial pO_2 and base deficit in some cases were evaluated on admission. A follow up of 48 hours was allowed for all these tests and for haematocrit fall and fluid sequestration. Thirty six (68%) of all patients had less than three signs, suggesting a mild pancreatitis, and 17 (32%) had three or more signs, suggesting severe acute pancreatitis. As many as 13 (76%) patients with confirmed haemorrhagic pancreatitis had three or more prognostic signs. Four patients with severe disease, however, showed less than three signs. Of the patients with mild pancreatitis, 89% (32/36) had less than three signs. The mean number of prognostic signs was 3·5 (±SD 1·8) in the patients with haemorrhagic pancreatitis and 1·2 (±SD 1·2) in the patients with a milder form of the disease. The prognostic signs in the different groups are presented in Table 4.

SERUM PHOSPHOLIPASE A_2

Serum phospholipase A_2 activities were already high

Table 4 *Prognostic signs per patient by severity of pancreatitis (n)*

	Haemorrhagic pancreatitis	*Fatal pancreatitis*	*Mild pancreatitis*	*Pseudocyst*	*Total*
0–1	2	–	21	1	23
2	2	–	11	–	13
3	7	1	2	–	9
4	2	1	2	–	4
5	2	1	–	–	2
6	1	–	–	–	1
7	–	1	–	–	–
8	1	–	–	–	1
Total	17	4	36	1	53
<3	4 (24%)		32 (89%)	1 (100%)	36 (68%)
≥3	13 (76%)	4 (100%)	4 (11%)		17 (32%)
$\bar{x}$+SD	3·5±1·8	4·8±1·5	1·2±1·2		1·9±1·7

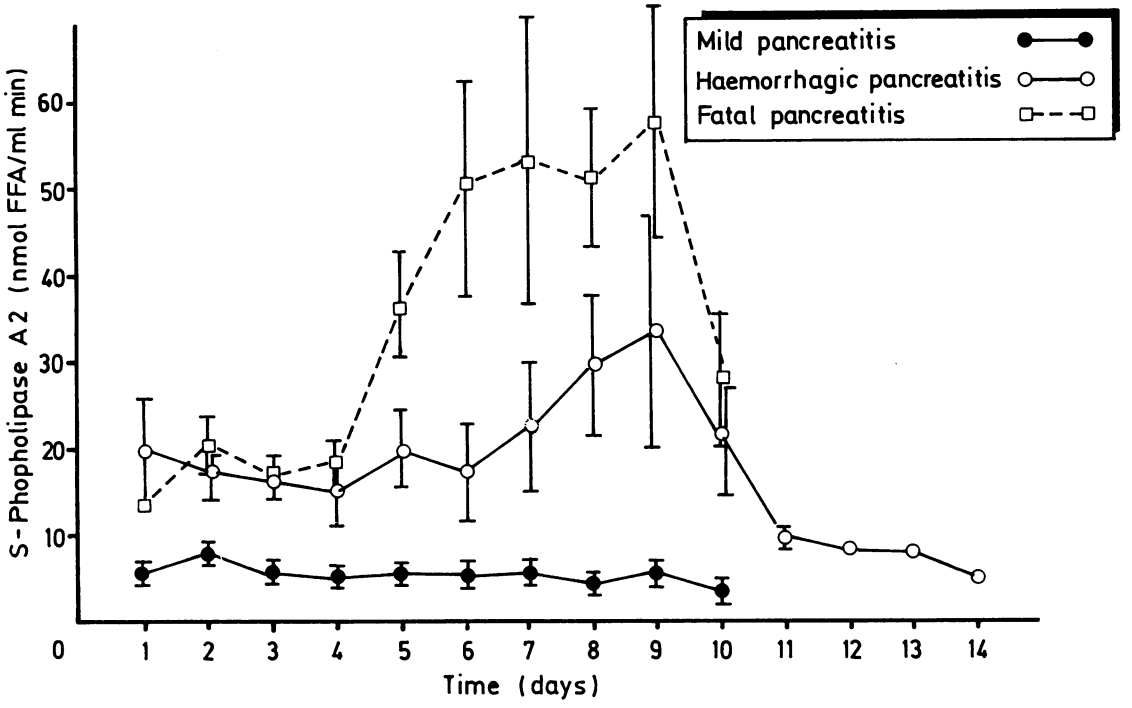

Fig. 2 *Serum phospholipase A_2 activity in the patients ($p<0{\cdot}001$). Values are mean±SEM.*

on admission in the patients with haemorrhagic pancreatitis (Fig. 2), and these rose to very high levels in all patients with haemorrhagic pancreatitis (up to 20–40 nmol FFA/ml min), especially in those who died (up to 50–60 nmol FFA/ml min). The serum phospholipase A_2 values returned to normal after the eleventh day of admission. There was only a slight increase in S-phospholipase A_2 activities in the patients with mild pancreatitis, all values being less than 10 nmol FFA/ml min. The difference in S-phospholipase A_2 activities between patients with mild and severe pancreatitis was significant ($p<0{\cdot}001$) even on the first day.

C-REACTIVE PROTEIN

The serum CRP values for the patients are presented in Figure 3. A rise in CRP values was seen in all groups. There was greater increase in CRP in the patients with acute haemorrhagic pancreatitis than in those with mild disease. The mean value of the CRP on the first day after admission was 280 mg/l (range 83–461 mg/l) in the patients with haemorrhagic pancreatitis and 45 mg/l (range <6–122 mg/l) in those with mild disease. This difference was statistically significant ($p<0{\cdot}001$). In only two patients with haemorrhagic pancreatitis was the CRP value on the first day less than 110 mg/l (83 and 106 mg/l) and in only two patients with mild pancreatitis more than 110 mg/ml (113 and 122 mg/l). The CRP values fell slowly in all patients, though remaining high until death in the patients with fatal pancreatitis. High CRP values correlated with the prognostic signs indicating severe pancreatitis (Fig. 4).

Discussion

One of the basic problems in treating patients with acute pancreatitis is to detect patients with a severe, haemorrhagic form of the disease as early as possible so that adequate treatment can be started immediately. Many efforts have been made to accomplish this early diagnosis, but no single test has proved reliable.[1,3,16,21] In 1974 Ranson *et al*[18] presented their early prognostic signs, which have later been modified by Imrie[21] and McMahon.[3] These signs, however, cannot be used to decide the treatment of an individual patient.[2,22] In the present study 76% of the patients with verified haemorrhagic pancreatitis had three or more prognostic signs. The aetiology of acute pancreatitis in Finland is predominantly alcohol, and the most severe cases are often young men as recently reported.[23,24]

Serum phospholipase A_2 activities are increased in acute pancreatitis.[7,10,22] Our previous studies suggested that the response to treatment correlated well with serum phospholipase A_2 activity.[10] On admis-

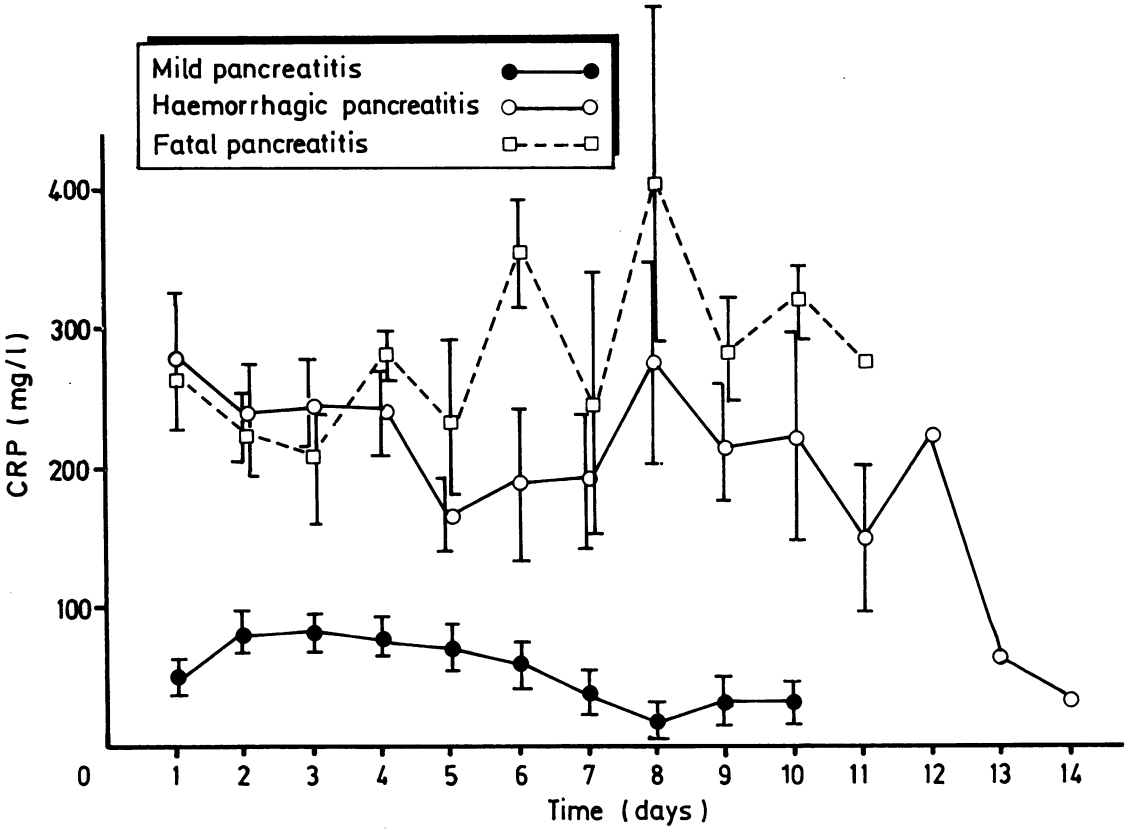

Fig. 3 *CRP values in the patients ($p<0.001$). Values are mean±SEM.*

sion the activity was not raised, suggesting that the assay is of no value for assessing the severity of the disease in the early stages.[10] In the present study, however, patients with haemorrhagic pancreatitis showed significantly higher ($p<0.001$) S-phospholipase A_2 activities on admission and during the first few days in hospital than did patients with mild disease. In the patients with mild pancreatitis, there was no increase in serum phospholipase A_2 activity, whereas in the patients with fatal haemorrhagic pancreatitis the increase in the enzyme activity was significant ($p<0.05$). Patients in whom the disease was fatal showed very high phospholipase A_2 activities (up to 60 nmol FFA/ml · min). In this study the S-phospholipase A_2 activities correlated with the severity of the pancreatitis, which suggests that this enzyme assay might have some prognostic value in the early assessment of the severity of the pancreatitis. The assay method used in this study is different from that used in the earlier studies.[22]

C-reactive protein is an 'acute phase protein', which is known as a non-specific and sensitive indicator of tissue injury, inflammatory response, and bacterial infection.[9,12,13] High CRP concentrations have been reported in various bacterial infections – for example, pneumonia, pyelonephritis, and tuberculosis.[13,25] The CRP is often higher in bacterial than in viral infections, a fact which is used clinically in the differential diagnosis of some infectious diseases.[25,26] C-reactive protein also rises in many inflammatory diseases such as rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, etc.[13,25] High concentrations are also seen in many neoplastic diseases.[25] Increased concentrations of CRP in patients with breast cancer are reported to indicate metastatic spread of the disease.[27] Serum CRP measurement also provides useful information in patients with myocardial infarction: there is an excellent correlation between the peak levels of CRP and creatine phosphokinase (CPK-MB).[13,25] Many intra-abdominal infections cause a rise in CRP.[25] Schentag *et al*[28] recently reviewed 97 patients with abdominal sepsis and concluded that CRP concentrations were not predictive of the type, site or severity of abdominal infection, but that, because persistent rises were frequently associated with new or unresolved

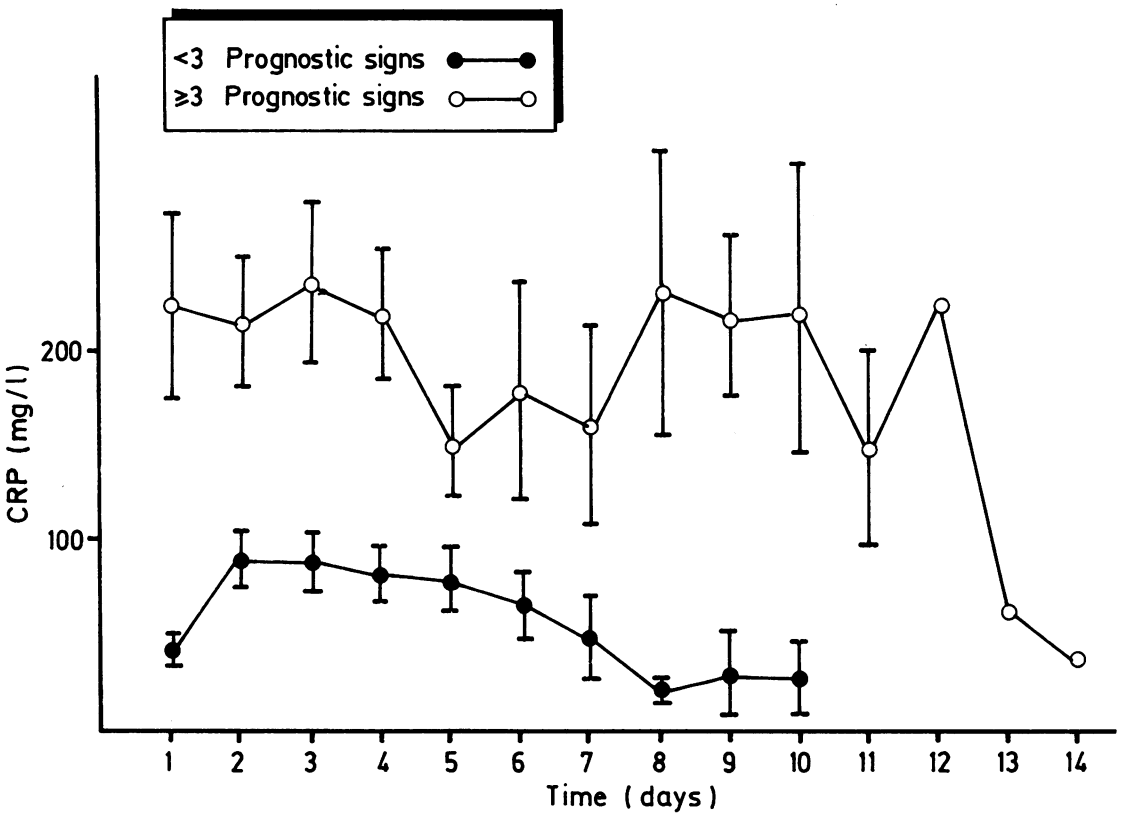

Fig. 4 *CRP values in the prognostic groups ($p<0{\cdot}001$). Values are mean±SEM.*

bacterial infections, serial determinations of CRP might be helpful in monitoring the course of the disease and response to treatment in patients with abdominal sepsis.[28] Serial CRP determinations have also been found helpful in the detection and monitoring of postoperative complications.[9 20] C-reactive protein is detectable in the serum within six hours of surgical trauma and usually peaks at 48 hours.[9 20 29] A decline in CRP values is usually noted on the third postoperative day,[20] and lack of a decline indicates some surgical complication involving infection.[9 13 20 30] Mayer *et al*[31] have recently studied the role of CRP in the assessment and monitoring of acute pancreatitis. They found that the main value of CRP is to provide a guide to the severity of inflammation and to indicate the patients' risk of developing pancreatic collections when the CRP values remain high (>100 mg/l) at the end of the first week of the illness.[31] Our patient with a pseudocyst had low CRP concentrations on admission and they remained low during hospitalisation (less than 10 mg/l). In this case the development of pancreatic pseudocyst could not be predicted by the rise in the CRP-values. Mayer also concluded that CRP could differentiate mild and severe attacks of pancreatitis better than the white blood cell count, erythrocyte sedimentation rate, body temperature or concentration of antiproteases.[31] McMahon *et al*[32] found low levels of CRP in patients with mild pancreatitis and high values in patients with severe pancreatitis.

Our results show significantly higher CRP concentrations already on admission in patients with haemorrhagic pancreatitis than in those with milder forms of the disease ($p<0{\cdot}001$). The diagnosis was verified at laparotomy in all patients. The difference remained significant during hospitalisation. The mean CRP value on admission was 45 mg/l in patients with mild pancreatitis and 280 mg/l in those with verified haemorrhagic pancreatitis. In only two patients with haemorrhagic pancreatitis was the CRP value on the first day less than 110 mg/l (83 and 106 mg/l) (range 83–461 mg/l) and in only two patients with mild pancreatitis more than 110 mg/l (113 and 106 mg/l) (range <6–122 mg/l). No infections causing raised CRP concentrations could be shown in these patients; neither could operative measures have increased

them, because the first samples were taken preoperatively on admission. Later, however, surgical procedures might partly be responsible for the high CRP values, because all patients with haemorrhagic pancreatitis underwent surgery.

In conclusion, in this prospective series of consecutive potentially severe attacks of acute pancreatitis, CRP values in different groups correlated well with the severity of the pancreatitis and with the prognostic signs, which suggests that CRP determinations are of value in the early assessment of the severity of acute pancreatitis. In the individual patient, however, the CRP values seem to provide a better measure of the severity of the disease than do the prognostic signs. The results are much the same as those given by the serum phospholipase A_2 assay, but the CRP assay is much easier to incorporate into the hospital routine.

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